NCDEU

TABLE OF CONTENTS

Oral Presentations

Tuesday, June 1 ..... page 1-18
Wednesday, June 2 ..... page 18-33
Thursday, June 3 ..... page 34-52
Friday, June 4 ..... page 52-53

Poster Abstracts Topic Index ..... page 54

*Poster Presentations ..... page 55-351

*Poster Number Index ..... page 352-378

*Presenting Author Index ..... page 379-395

*Odd-Numbered posters are being formally presented on Wednesday
Even-Numbered posters are being formally presented on Thursday

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Tuesday, June 1, 2004 (continued)

WORKSHOP 1
Recruitment in the Community: Challenges and Opportunities for Clinical Trials
9:00 a.m. - 12:00 p.m.

Overview

Treatment success in clinical settings has often failed to match the promise of newly introduced agents. A key factor is the failure to include populations in clinical trials that are representative of our increasingly diverse country. Ethnic minorities and women are often under represented both as patients or investigators. Common comorbidities such substance abuse are excluded from studies. This workshop will discuss the formidable challenges and success in recruiting and implementing clinical trials with representative populations and in community settings. The implications of such issues as ethnic psychopharmacology and comorbidity will be discussed.

Recruitment of African Americans: Barriers and Successes at Multiple Sites

William B. Lawson, M.D., Ph.D.
Howard University

INTRODUCTION: African Americans are underrepresented in clinical trials. Recruitment difficulties, perhaps related to mistrust of research, is an often stated reason. We are reporting the outcome of a multifaceted recruitment effort by African American (AA) researchers at an Historically Black University in a heavily AA inner city community.

METHOD: Howard University (HU) was funded to collaborate with the NIMH intramural Mood and Anxiety program to increase ethnic diversity in NIMH trials and later Howard studies.

RESULTS: After two years, primarily in the past six months, 150 subjects were screened for participation in over 20 protocols, mostly at NIMH, excluding a study of normal volunteers. Recruitment occurred at a psychiatry inpatient, and outpatient unit, and through ads. Thirty actually entered into clinical trials, infusion, and imaging studies at NIMH. Barriers included distrust, distance, economic hardship, and general medical conditions such as hypertension and HIV that are disproportionate in inner city AA. Over 70% of bipolar and depressed inpatients were excluded due to substance abuse. A protocol involving comorbidity was later implemented at Howard. Radio and TV were far more effective in recruitment for studies of mood disorders vs. anxiety disorders while a free newspaper was effective for anxiety disorders. Recruitment from an HU primary care clinic yielded 300 patients for an HU study of which half were actually enrolled.

CONCLUSION: Recruitment of AA for studies in biological psychiatry may be difficult but not impossible given appropriate resources and adequate addressing of key barriers.

Educational Objectives:

- Determine barriers to recruitment of ethnic minorities.
- Identify recruitment approaches most successful for a multiethnic population.
- Appreciate the practical issues in implementing a biologically based psychiatric protocol in ethnic diverse communities.

WORKSHOP 1 (continued)
Recruitment in the Community: Challenges and Opportunities for Clinical Trials
9:00 a.m. - 12:00 p.m.

The Hispanic Initiative Program for Mood Disorder Patients at the Intramural Program of the National Institute of Mental Health: Recruitment Efforts and Findings

Carlos A. Zarate, Jr., M.D.
National Institute of Mental Health

According to the World Health Organization, depression is the leading cause of disability in the United States today. While much is known about mood disorders in the general population, a dearth of knowledge exists regarding mood disorders in the Hispanic population, currently the largest minority group in the United States. We present the results of an ongoing initiative to recruit and study Hispanic patients with mood disorders into an Experimental Therapeutics Program.

METHOD: Several phases were implemented for the development of this Research Program (planning, recruitment/screening phase and study, and aftercare phase). Some of the issues addressed in implementing this program included the ethics of conducting research on this population, staff training (ability of speak Spanish and cultural sensitivity), the use of valid diagnostic and rating instruments translated into Spanish, selecting the most appropriate media for advertising the program, consenting monolingual Spanish speaking patients, the monitoring of adherence to the assigned treatment, psychosocial problems, and assuring that appropriate Aftercare was in place.

RESULTS: The initiative began at the end of May 2002. From May 2002 to April 2004, the number of phone screens conducted had reached 600. 66 face-to-face screens were completed, and 32 Hispanic patients were consented for an experimental treatment study. Misdiagnosed mood disorders, undertreatment and mistreatment, access to medical care, psychosocial issues, problems with adherence to appointments and treatment were identified as ongoing issues in the research of Hispanic patients.

CONCLUSIONS: This data suggests that the Hispanic community has specific characteristics that should be taken into account when implementing an Experimental Therapeutics Research Program in mental health. Such a program is feasible and to date has been well received by the patients, their families, and the Hispanic community as demonstrated by their willingness and motivation to participate in research.

Learning Objectives:

- To understand the different barriers Hispanics face when trying to access mental healthcare.
- To describe the strategies implemented for recruiting Hispanic patients into mood disorder treatment research studies.
- To understand different psychosocial issues in Hispanic patients and their impact on patient recruitment and compliance.

WORKSHOP 1 (continued)
Recruitment in the Community: Challenges and Opportunities for Clinical Trials
9:00 a.m. - 12:00 p.m.

Recruiting African Americans from Primary Care and Community Settings

DiAnne Bradford, Ph.D.
Morehouse School of Medicine

Research in the mental health arena was initiated just six years ago at Morehouse School of Medicine. Reflecting the school's mission of conducting research in the medically under served, the Minority Mental Health Research Program has focused on conducting the highest standard of research in African Americans parallel with exposure and training of young African-American undergraduates, residents and faculty in the art, ethics and science of conducting research. Studies have included screening and treatment of depression in a primary care setting; population pharmacogenetic studies; and genetic etiology studies, most of which had highly successful recruitment rates. Lessons have been learned from both our successes and failure. Key issues in successful recruitment among African Americans are investigators and mission, selection and training of study personnel, frequent training and constantly monitored cultural competency, involvement in the community, and partnering with external organizations.

Objectives:

1. Learn key issues in cultural competency in conducting mental health studies in minority populations.
2. Identify potential recruitment "partners" in the community, private and state entities.

WORKSHOP 2
Anticonvulsants in Mental Disorders: Translational and Treatment Research
9:00 a.m. - 12:00 p.m.

Overview

Many anticonvulsants are known to target GABAergic or glutamatergic systems in the central nervous system. These compounds increasingly used in the treatment of various mental disorders. This workshop syntheses the recent mechanistic findings with emerging clinical efficacy data to provide new insights in the role of GABA and glutamate in mental disorders.

Why Do Anticonvulsants Play a Role in the Treatment of Schizophrenia and Mood Disorders? A Systems Neuroscience Perspective

John H. Krystal, M.D., Gerard Sanacora, M.D., Ph.D., Hilary Blumberg, M.D., D. Cyril D'Souza, M.D.; Daniel Mathalon, M.D., Ph.D., Graeme Mason, Ph.D.; Idil Cavus, M.D., Ph.D.
Yale University School of Medicine, Schizophrenia Biological Research Center and Mood Disorders REAP, VA Connecticut Healthcare System (116-A), Abraham Ribicoff Research Facilities, CMHC

This presentation will focus on mechanisms related to the regulation of cortico-limbic networks that might shed light on the efficacy of anticonvulsant medications for treating schizophrenia, bipolar disorder, and major depression. Briefly, human intracortical microdialysis data suggest that glutamatergic hyperactivities interferes with functional synchrony within cortical networks. In schizophrenia, glutamatergic hyperactivity may arise as a consequence of deficits in GABA neurons or reductions in NMDA receptor function. This hyperactivity may be modeled in animals and humans using NMDA antagonists. The cognitive impairments and psychosis associated with acute blockade of NMDA receptors may be attenuated by pretreatment with several classes of agents (lamotrigine, L-type calcium channel antagonist, group II mGluR agonists) that reduce glutamate release or the postsynaptic effects of glutamate. These data support the efficacy of lamotrigine augmentation of neuroleptic treatment for schizophrenia. The network pathology in mood disorders differs from schizophrenia. There is interest in the possibility that effective antimanic anticonvulsants may depress glutamatergic excitability by blocking a variety of ion channels or by attenuating facets of signal transduction downstream from excitatory mechanisms, such as attenuating protein kinase C function. In depression, loss of glia may increase extrasyn aptic levels of glutamate, depressing synaptic glutamate release. By depressing the accumulation of extrasynaptic glutamate, lamotrigine, riluzole, and other anticonvulsants that reduce glutamate release may paradoxically restore synaptic function within glutamatergic networks. This paradoxical "stimulatory" effect on synaptic glutamate function may help to explain the limited efficacy of lamotrigine in treating mania.

Objectives:

- Discuss the regulation of cortico-limbic networks on the efficacy of anticonvulsant medications in schizophrenia, bipolar disorder, and major depression.
- Provide preclinical evidence for a role of GABA and glutamate in treatment of mental disorders.

WORKSHOP 2 (continued)
Anticonvulsants in Mental Disorders: Translational and Treatment Research
9:00 a.m. - 12:00 p.m.

Efficacy of Anticonvulsants in Bipolar Disorders: Novel Findings from Longitudinal Studies

Terence A. Ketter, M.D.
Stanford University

Anticonvulsants have heterogeneous psychotropic profiles and mechanisms of action. Although systematic evidence linking clinical and mechanistic differences is lacking, some patterns (such as GABAergic agents being more sedating, and antiglutamatergic agents allowing weight loss) are beginning to emerge. Clinically, anticonvulsants can be classified as those stabilizing mood 'from above baseline' by preventing episodes of mania and those stabilizing mood 'from below baseline' by preventing episodes of depression (Ketter and Calabrese 2002). This new nomenclature has been proposed to facilitate the development of mood stabilizers and inform the use of medications in combination. Older active comparator-controlled data suggest carbamazepine may have some efficacy in maintenance treatment. Limited data also suggest that combinations of lithium or olanzapine with carbamazepine or divalproex may be useful in prophylaxis. Newer placebo-controlled maintenance data were published during 2003 for lamotrigine (Bowden et al 2003, Calabrese et al 2003) and divalproex (Gyulai et al 2003). For patients with bipolar disorder whose course is primarily characterized by depression, lamotrigine is recommended because of its acute and long-term efficacy in depression. For patients whose course is primarily characterized by mania, divalproex is recommended because of its acute and long-term efficacy in mania. To date, there do not appear to be any anticonvulsants that possess equal efficacy in both phases. The majority of patients with bipolar disorder tend to need combination therapy with one agent that works 'from above' and another that works from below' baseline. The available evidence suggests that divalproex possesses marked efficacy in mania with mild to moderate efficacy in depression and that lamotrigine has the opposite profile with marked efficacy in depression and mild to moderate efficacy in mania. Randomized controlled studies are ongoing that evaluate the safety and efficacy of these two anticonvulsants in combination.

Objectives:
- Review placebo-controlled maintenance evidence on anticonvulsants in bipolar disorder.
- Discuss the lack of a well-defined "class effect" in the treatment of bipolar disorder and differentiate the efficacy profiles of the anticonvulsants commonly prescribed in bipolar disorder.

Advances in Glutamate-based Adjunctive Anticonvulsant Treatments in Schizophrenia: Implications for Clinical Pharmaco-Management

Serdar Dursun, M.D., Ph.D.
University of Manchester, United Kingdom

It is widely accepted that schizophrenia is the most heterogeneous of all psychiatric disorders. It remains "the worst disease affecting mankind, even AIDS not excepted" (Editorial, Nature 1988, 95). Almost all known anticonvulsant drugs, and many other psychotropics, have been examined as "adjunctive" treatments in schizophrenia, with limited success. Recent advances indicate a more predominant role of glutamate in experimental psychosis and schizophrenia. This finding lead to the trials of lamotrigine, (an anticonvulsant with unique mechanism of action on glutamate neurotransmission) as an adjunctive treatment in schizophrenia. The aim of the presentation will be to review primarily the evidence for glutamate-based adjunctive anticonvulsant treatments in schizophrenia.

Objectives:
- Review the primary evidence to support the use of anticonvulsants as adjunctive therapy in schizophrenia.
- Discuss the role of glutamate in psychosis associated with schizophrenia.

WORKSHOP 2 (continued)
Anticonvulsants in Mental Disorders: Translational and Treatment Research
9:00 a.m. - 12:00 p.m.

Anticonvulsants and Other Glutamatergic Modulators in Alzheimer's Disease

Saleem Ismail, M.D.
University of Rochester

Neuropsychiatric disturbances are integral features of Alzheimer's disease and represent a major public health concern and effective therapy is needed. Agitation is particularly distressing to caregivers and frequently co-occurs with psychosis. Several pharmacological agents that target glutamatergic and GABAergic systems have shown promise in treatment of neuropsychiatric conditions. Among mood stabilizers carbamazepine and valproate have been most extensively studied to treat agitation in dementia. Recently memantine, a low to moderate affinity uncompetitive NMDA receptor antagonist, became available in US for treatment of moderate to severe AD. The evidence from clinical trials is mixed, with some trials showing benefit and others with negative or null results. There is insufficient evidentiary data to guide clinical practice. On the other hand, there are relatively few adequately defined chronic treatments of any kind for agitation in dementia, and none which have been recognized by the FDA. This presentation will review available evidence from clinical trials of anticonvulsants and memantine for neuropsychiatric disturbances in dementia. Recent basic and preclinical work suggests that valproate may have effects on cellular signaling pathways that could be beneficial in the long-term treatment of Alzheimer's disease. These concepts have been combined in a novel clinical trial that will address whether chronic valproate administration will delay emergence of agitation, slow cognitive decline or produce measurable changes in biochemical pathways that may lead to an improved understanding of the mechanism of action of this drug.

Objectives:

- Discuss clinical and preclinical rationale for use of anticonvulsants and other glutamatergic modulators in Alzheimer's disease and associated behavioral symptoms.
- Discuss evidence from clinical trials regarding symptomatic effects of anticonvulsants and memantine for treatment of behavioral symptoms in dementia.
- Discuss rationale for a novel clinical trial using valproate to delay, attenuate or prevent emergence of agitation in patients with Alzheimer's disease.

Workshop 2 (continued)
Anticonvulsants in Mental Disorders: Translational and Treatment Research
9:00 a.m. - 12:00 p.m.

Anticonvulsants in Anxiety, Unipolar Depression and Eating Disorders

James G. Barbee, IV, M.D.
Louisiana State University Health Sciences Center
George C. Dunn, M.D.
Louisiana State University Health Sciences Center/LSU Behavioral Sciences Center/LSU Anxiety and Mood Disorders Clinic

The efficacy of the anticonvulsants in bipolar disorder has been widely accepted for many years. Given the diversity of their structures and presumed mechanisms of action, it is perhaps no surprise that reports have emerged regarding the possible effectiveness of these agents in a wide variety of other psychiatric illnesses, including anxiety disorders, unipolar depression and eating disorders. The quality of this evidence varies tremendously, however, from that available in published studies of large multi-center placebo-controlled trials to case reports of single patients. Thus far, the efficacy of pregabalin in generalized anxiety disorder (and possibly other anxiety disorders) seems well established. Gabapentin has been shown to be effective in social anxiety disorder in double-blind, placebo-controlled trials. Lamotrigine may be effective as an antidepressant augmentation agent in unipolar depression. Eating disorders, particularly binge eating disorder and bulimia nervosa, may respond to topiramate.

The current state of knowledge regarding the efficacy of the anticonvulsants as a group will be surveyed in anxiety disorders, unipolar depression, and eating disorders. Emphasis will be placed upon the strengths and weaknesses of the current studies that are available. Directions for future research will also be discussed.

Objectives:

- Survey the state of current evidence from both published and unpublished sources regarding the efficacy of the anticonvulsants in anxiety, unipolar depression, and eating disorders.
- Discuss possible directions for future research on the use of anticonvulsants in these indications.

Tuesday, June 1, 2004 (continued)

WORKSHOP 3
Enhancing Precision in Clinical Trials VII
9:00 a.m. - 5:00 p.m.

Overview

The objective of this panel is to present theoretical, methodological, and technological advances that may increase precision in clinical trials in the context of what has been learned from past experiences and modeling in clinical trials.

This all-day workshop brings together thought leaders from academia, government, and industry to discuss practical experience and theoretical, methodological, and technical advances intended to enhance precision in clinical trials. Ample time is included for audience participation.

A Novel Study Design to Reduce the Placebo Response Rate: The "Sequential Parallel Comparison Design"

Maurizio Fava, M.D.
Massachusetts General Hospital

The placebo response is a major issue in clinical trials for psychiatric disorders. This presentation will briefly review possible contributing factors to this issue and various proposed remedies, whose helpfulness ranges from minimal if any to significant. The presentation will then focus on the “Sequential Parallel Comparison Design, ”a novel study design for double-blind, placebo-controlled trials in psychiatric disorders. This design is aimed at reducing both the overall placebo response rate and the sample size required for such trials. Although its usefulness in clinical research needs to be tested empirically, if this study design were to be found to meet its stated goals, this could markedly facilitate the process of clinical development of new compounds for the treatment of psychiatric disorders. The basic idea is to have two phases of treatment. The first phase involves an unbalanced randomization between placebo and active treatment with more patients randomized to placebo. In the second phase, non-responders treated with placebo are randomized to either active treatment or placebo. Since patients on the second phase have already ‘failed placebo’, their placebo response will be reduced. The analysis pools the data from both phases in order to maximize power and reduce the required sample size.

Reference: Fava M, Evins AE, Dorer DJ, Schoenfeld DA. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. Psychother Psychosom. 2003 May-Jun;72(3):115-27.

Objectives:

- Participants will become familiar with the most common contributing factors to high placebo response rates in clinical trials of psychiatric drugs.
- They will also learn the basic limitations of the currently used study designs.
- Finally, they will become familiar with a novel study design aimed at reducing the overall placebo response rate in such clinical trials.

WORKSHOP 3 (continued)
Enhancing Precision in Clinical Trials VII
9:00 a.m. - 5:00 p.m.

Development and Evaluation of the Quick Inventory of Depressive Symptoms (QIDS)

A. John Rush, M.D.
University of Texas Southwestern Medical Center

The development of a brief, clinician efficient measure of depressive symptom severity measure that can be used to identify treatment effects in controlled trials and to monitor efficiently response to treatment in routine practice would enhance the translation of clinical research findings into practice and vice versa. The 16-item Quick Inventory of Depressive Symptoms (QIDS) is a self-report and a clinician rating that can also be acquired by an automatic telephone patient interview (IVR). This presentation reviews new findings that relate each of these 3 versions of the QIDS to each other and to a telephone based live interview that collected the 17-item Hamilton Rating Scale for Depression using a semi-structured interview. In brief, all 3 versions of the QIDS demonstrate acceptable psychometric properties. Results with the IVR QUIDS closely matches results obtained by clinician rating and self-report using data from Level 1 of the STAR*D Trial. Conversion tables relating HRSD17 total scores to QIDS total scores have been generated. The QIDS-IVR or QIDS-SR provide clinically efficient measures that should reduce the cost of outcome trials, and facilitate the regular measurement of symptoms in daily practice.

Education Objectives:

1. To understand the rationale underlying the development of the 16-item Quick Inventory of Depressive Symptoms.
2. To understand the psychometric properties of the QIDS obtained by clinician rating, self-report, and the interactive voice response system (IVR) using classical test theory.

IVR Evolved

John H. Greist, M.D.
Healthcare Technology Systems

Interactive voice response (IVR) is a mature technology familiar to all, though seldom recognized by name. There is widespread administrative use of IVR in randomized clinical trials (RCTs) of pharmaceutical agents for randomization, drug inventory control and reporting of serious adverse events. IVR clinical applications that gather information from and give information to study subjects are growing rapidly.

Focused on clinical IVR applications in RCTs, this presentation addresses fundamental concerns about clinician versus IVR self-report assessments by reviewing data from seven RCTs where comparisons were made. IVR applicability in challenged populations (e.g., advanced age, psychosis and dementia) will be discussed. Obstacles to appropriate use will be identified and possible solutions offered.

Learning Objectives:

1. Review data on rater bias at baseline from five RCTs comparing clinician and IVR self-report ratings.
2. Evaluate effects of IVR assessments on signal detection.
3. Consider advantages and limitations of IVR assessments for subjects with advanced age, psychosis and dementia.

WORKSHOP 3 (continued)
Enhancing Precision in Clinical Trials VII
9:00 a.m. - 5:00 p.m.

Advancing Safety Evaluations in Psychiatric Drug Trials: An FDA Perspective

Thomas Laughren, M.D.
Food and Drug Administration

Fully exploring the safety of psychiatric drug products is an important goal of registration trials. This talk will briefly review regulatory principles and practices in safety evaluation, and then focus more specifically on two challenging aspects of safety evaluation: (1) optimal approaches to collecting safety information, and (2) coding of adverse events. Two examples of recent failures in ascertainment in psychiatric drug trials will be provided: (1) sexual dysfunction with SSRIs, and (2) suicidality in pediatric antidepressant trials. Problems in coding adverse event data will be explored, including lumping dissimilar terms, splitting similar terms, and coding to the wrong preferred term. Approaches to improving safety ascertainment and coding practices will be explored.

Educational Objectives:

1. Understand regulatory principles and practice in safety evaluation for psychiatric drugs.
2. Understand problems with safety assessments in psychiatric drug studies, and possible solutions.
3. Understand problems with coding of adverse event data in psychiatric drug studies, and possible solutions.

WORKSHOP 4
NIMH-Funded Multisite Clinical Trials in Children and Adolescents with Depressive and Anxiety Disorders
9:00 a.m. - 5:30 p.m

Overview

NIMH multisite trials testing the effects of treatment interventions for children and adolescents with depressive and anxiety disorders will be presented. The purpose is to inform on the results of recently completed studies and on the design and methods of currently ongoing activities. Research efforts in this area can be articulated around the following major questions:

- How do pharmacological treatment and cognitive-behavioral therapy (CBT) for adolescents with major depression compare to each to other and to their combination? The Treatment for Adolescents with Depression Study (TADS), which randomized about 440 youths with major depression, addresses this question. The TADS primary efficacy and safety results will be presented.

- What should the second line of treatment be for adolescents with depression who have not improved with an adequate trial of selective serotonin reuptake inhibitor (SSRI) antidepressant? The Treatment of Resistant Depression in Adolescents (TORDIA) is an ongoing multisite trial to compare alternative antidepressant medication, as monotherapy or in combination with CBT.

- How does treatment with SSRI medication compare with cognitive-behavioral therapy in the treatment of children and adolescents with obsessive-compulsive disorder (OCD)? How does each single treatment modality compare with their combination? The Pediatric OCD Trial has been recently completed and results will be presented.

- How do pharmacological, psychotherapeutic, and combined interventions for children and adolescents with anxiety disorders (generalized anxiety, social phobia and separation anxiety) compare to each other? The Child Anxiety Multimodal Study (CAMS) is currently in progress to address this question? Design and methods will be presented.

- How to develop and pilot test treatment interventions for adolescents who have recently made a suicidal attempt? One of the groups of the Research Units on Pediatric Psychopharmacology and Psychosocial Interventions (RUPP-PI) network will present the protocol of the Treatment of Adolescent Suicidal Attempters (TASA).

Tuesday, June 1, 2004 (continued)

TREATMENT DEVELOPMENT SESSION I
Negative and Deficit Symptoms as Treatment Targets in Schizophrenia Therapeutics
9:00 a.m. - 11:00 a.m.

Overview

Deficits in social functioning are a core symptom of many neuropsychiatric disorders, including schizophrenia and autism. These deficits often present prior to overt disease, are typically in evidence throughout the course of the disease, frequently affect long-term outcome and are often the most treatment-resistant aspects of the syndromes. General cognition - the ability to recognize, interpret and manipulate one's environment both concretely and theoretically - plays an important role in supporting social behavior; however, its overall contribution to psychosocial functioning is modest. Social cognition, in contrast, refers specifically to the mental operations subserving social interactions, the ability to interpret emotions and intentions, and the ability to empathize with others. These aspects of social behavior are not readily assessed by traditional neurocognitive tools. The relationship to negative symptom pathology is not understood.

The purpose of this workshop is to define negative symptom, neurocognition, and social cognition constructs, to review the assessments that currently exist and those in development, and to examine the effect of novel therapies. The first portion of the workshop will develop a problem statement, identifying neuropsychiatric diseases characterized at least in part by deficits in social competence and indicating how these deficits affect outcomes. The second portion of the workshop will further develop definitions of social cognition, review the instruments and procedures that are available to assess it, and begin to elucidate its neural basis. The final portion of the workshop will present data from ongoing clinical trials which seek to assess the impact of novel pharmacological manipulations on these constructs including social functioning in autism and schizophrenia. Data from a soon-to-be unblinded Phase 3 study in autism will be included.

WORKSHOP 5
Ethical Challenges in Clinical Research
1:00 p.m. - 4:00 p.m.

Despite the complex nature of the clinical research enterprise with its many stakeholders, the relationship linking investigators and research participants remains special. The ethical nature and boundaries of this investigator-subject relationship and the obligations that derive from it are currently in flux. Nevertheless, from the design of clinical research to the enrollment of research participants to the handling of research information, investigators must bear in mind their ethical obligations to the individuals who will participate in the research. This workshop will address real-life issues in the responsible conduct of mental health research with the aim of framing ethical research as an ongoing decision-making process at all levels of the research endeavor, rather than merely as a compliance chore designed to meet legislative and regulatory requirements. Presenters will briefly identify issues commonly arising in mental health research, followed by case studies through which workshop participants will have the opportunity to discuss and debate the nature of investigator obligations to research participants. The purpose of the workshop is to engage participants in an interactive discussion of the ethical issues and dilemmas common to mental health research and the principles and decision-making processes central to the responsible conduct of research.

WORKSHOP 5 (continued)
Ethical Challenges in Clinical Research
1:00 p.m. - 4:00 p.m.

Should the Blind Treat the Blind After Subjects Participate in a Clinical Trial?

Joseph C. Blader, Ph.D.
Stony Brook State University of New York

Subjects in controlled clinical trials obtain experience with study-provided treatment that could inform their further therapy by awareness of the efficacy or inefficacy of the study treatment they received. However, after they participate in blinded trials, patients typically do not learn what treatment they actually received during the study. This article examines ethical aspects of withholding treatment assignment information from subjects after they participate in a blinded clinical trial and who require ongoing medical care. Keeping investigators and subjects blind to treatment allocation throughout a trial is a key element of clinical research methodology, but the value of keeping participants and their medical providers blinded after participation is less certain and may pose risks that include delay in the receipt of efficacious care, exacerbation of symptoms, or prolonged exposure to superfluous or toxic treatment. The significance of these risks is likely to vary with the specific disease and the time course of its response to available therapies. Currently, it seems appropriate for investigators a) to evaluate the risks of keeping subjects blind after participation, b) to justify doing so in relation to serious, identifiable risks to the study's validity, and c) to apprise prospective subjects clearly that information about their response to specific treatment during the trial will not be available to guide their post-study care. In the long-run, research on the impact that keeping subjects uninformed about study treatment has on post-study patient outcomes and on study integrity can foster the development of procedures that optimally balance both.

WORKSHOP 6
New Strategies for Measuring Outcomes in Clinical Trials in Mood Disorders
1:00 p.m. - 5:00 p.m.

Overview

A key to achieving successful clinical trials for mood disorders is to develop optimal strategies for measuring outcomes. Outcome measurement can be improved by using complementary approaches at several steps in the conduct of a trial: 1) improvement of rater training and application of new ratings technology to obtain more consistent measurements of clinical change; 2) development of methods to restrict the number of placebo responders enrolled in trials in order to more effectively detect medication efficacy; 3) application of new methods for integrating and managing data collected in a trial to enhance data reliability; and, 4) refinement of the definitions of treatment outcome endpoints (i.e., definition of remission). Presenters in this workshop will describe the innovative methods and technologies they have developed in each of these areas in an effort to enhance the accuracy of outcomes measurement in clinical trials for mood disorders.

WORKSHOP 6
New Strategies for Measuring Outcomes in Clinical Trials in Mood Disorders
1:00 p.m. - 5:00 p.m.

Key Factors Affecting Ratings Accuracy in Clinical Trials

Steven D. Targum, M.D.
PharmaStar

Mark West, M.D.
PharmaStar

Ratings accuracy is a lynchpin in the achievement of successful CNS clinical trials. The nuances inherent in the evaluation of patients with mood disorders and the ability to recognize meaningful clinical change during a clinical trial requires an experienced clinician. Skilled raters need to understand the disease under study, the protocol design, the rating instrument and its applicability for the specified study population, and be able to establish rapport with patients who may or may not be cooperative. Inter-rater reliability is challenged by inexperienced raters, the need for multiple language formats in global trials, and interpretative ratings biases that may alter scores between different cultural groups. Although the measurement of meaningful clinical change may always need raters who interact in-person with a patient, innovative technologies are being developed that may enhance accuracy via computer-assisted interviews or remote data collection.

In this presentation, the interplay between the patient, the rater, and the rating instrument will be explored using video vignette examples from real patient interviews in order to demonstrate and consider the complexity entailed in obtaining accurate symptom ratings.

WORKSHOP 6 (continued)
New Strategies for Measuring Outcomes in Clinical Trials in Mood Disorders
1:00 p.m. - 5:00 p.m.

A Method for Enhancing Human Rater Performance: The Interactive Computer Interview

Noreen A. Reilly-Harrington, Ph.D.
Concordant Rater Systems and Massachusetts General Hospital/Harvard Medical School
Daniel DeBonis
Concordant Rater Systems
Roy Perlis, M.D.
Concordant Rater Systems and Massachusetts General Hospital/Harvard Medical School
Daniel Lewis, J.D.
Concordant Rater Systems
Mary Ann Palko, M.Ed.
Concordant Rater Systems
Andrew C. Leon, Ph.D.
Weill Medical College of Cornell University
Gary S. Sachs, M.D.
Concordant Rater Systems and Massachusetts General Hospital/Harvard Medical School

This presentation will describe a patented, automated system that can monitor the quality of clinical rating scales administered by humans by conducting an evaluation independent of that done by a human rater. The Interactive Computer Interview (ICI) is a self-rated, computerized interview that utilizes an algorithm of probes designed to assign symptom severity ratings. The goal of the ICI is not to replace the human rater, but to enhance the sensitivity and consistency of human raters by using the ICI as a "check" on the ratings generated by live raters. CRS has developed versions of the ICI for depression (based upon the Montgomery Asberg Depression Rating Scale) and for mania (based upon the Young Mania Rating Scale).

In this study, 100 patients with a diagnosis of Bipolar I or II Disorders (ages 19-71) completed both a live interview of the YMRS with a human rater (LR) and the ICI-M, in counterbalanced order. A panel of expert raters reviewed each videotaped LR and assigned a consensus rating (CR).

Intraclass correlation coefficients (ICCs) were .91 between the ICI-M and CR and .97 between the Live interview and CR, providing empirical support for the validity of each approach. Coefficient alphas indicated comparable internal consistency reliability: ICI-M=.82, LR =.83, and CR=.84. Mean scores of each method were as follows: ICI-M=24.7, LR =21.3, CR=20.9. The ICI-M was significantly more sensitive than the LR ($p<.001$) and the CR ($p<.001$), and resulted in significantly higher ratings than CR on mood, speech, psychotic content, and disruptive-aggressive behavior.

WORKSHOP 6 (continued)
New Strategies for Measuring Outcomes in Clinical Trials in Mood Disorders
1:00 p.m. - 5:00 p.m.

Improving Outcomes of Phase IIa and IIb Clinical Trials for Depression

Andrew F. Leuchter, M.D.
UCLA Neuropsychiatric Institute
David J. DeBrota, M.D.
Lilly Research Laboratories

The placebo response is a significant confound in phase IIa (small proof of concept) and phase IIb (potentially pivotal) studies of antidepressant medications. High placebo response rates make it challenging to determine if putative antidepressants have significant efficacy and which of several compounds should be carried forward to phase III (larger scale efficacy trials). A variety of biologic and psychological measures may be useful in identifying likely placebo responders prior to enrollment in phase II trials. These include quantitative electroencephalography (QEEG) or other brain imaging techniques, polysomnography, reaction or cognitive processing time measures, genotyping, and other biometric measures. Data suggest that multiple biological and psychological measures could be combined to establish an endophenotype of a likely placebo responder. It might be possible to utilize restrictive entry criteria to exclude such subjects from phase II trials and thereby reduce placebo response rates. If placebo response rates were reduced, phase II trials could be conducted more effectively and efficiently and could yield more reliable data to inform decisions regarding phase III medication development.

Bridging Psychiatry, Psychology, Medical Informatics, and High Technology: A Web-based Survey and Research Management System for the CPT-III Project

Elizabeth Miller, Ph.D.
DatStat Inc.
Steven D. Hollon, Ph.D.
Vanderbilt University
Jan Fawcett, M.D.
University of New Mexico

This presentation will explore advances in the application of web-based methodologies for collecting, managing, analyzing, and reporting clinical trial data. The design, development, and deployment of a web-based research management system will be discussed in the context of the CPT-III Project. The CPT-III Project is an ongoing, large, multi-site NIMH-supported clinical trial between Rush Medical Center, The University of Pennsylvania, and Vanderbilt University for the prevention of recurrence in depression with drugs and cognitive therapy. The goal of this discussion is to communicate the advantages and considerations of utilizing a web-based system and its impact on data collection and access, project management, and patient care. Web-based data management systems may prove considerably more beneficial than current paper and/or computer based methods and provide an unprecedented opportunity to expedite the research process (both in terms of accuracy and collaboration) and enhance responsiveness to patient concerns.

WORKSHOP 6 (continued)
New Strategies for Measuring Outcomes in Clinical Trials in Mood Disorders
1:00 p.m. - 5:00 p.m.

Defining Remission from Depression

Mark Zimmerman, M.D.
Rhode Island Hospital
Michael A. Posternak, M.D.
Rhode Island Hospital
Iwona Chelminski, Ph.D.
Rhode Island Hospital

In antidepressant clinical trials, remission from depression is usually defined according to post-treatment scores on the symptom severity measures such as the Hamilton Rating Scale for Depression (HRSD) or the Montgomery-Asberg Depression Rating Scale (MADRS). However, it is not clear what cut-offs should be used on these measures to define remission.

The Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project has examined the question of defining remission. The group has analyzed cut-off scores on the 17-item HRSD and 10-item MADRS to determine how closely these scores correspond to the DSM-IV definition of remission. They also examined the relation of cut-off scores to the percentage of depressed outpatients in ongoing treatment who are considered to be in remission, and the association between remission status and psychosocial impairment. The data suggest that lower cut-off scores than those most commonly used to define remission on the scales seem to be more valid.

Tuesday, June 1, 2004 (continued)

TREATMENT DEVELOPMENT SESSION 2
Metrics: Methodological Issues in Clinical Trials Targeting Cognition in Schizophrenia
3:30 p.m. - 5:00 p.m.

Overview

This session will provide an update of the activities of the NIMH MATRICS (Management and Treatment Research to Improve Cognition in Schizophrenia) initiative to support the development of pharmacological agents to improve neurocognition in schizophrenia. Dr. Fenton will describe the background of the MATRICS intitiative and the NIMH approach to stimulating drug development in an important clinical area. Dr. Green will describe the development of a neuropsychology battery to measure cognition in trials of putative cognition enhancing drugs. Dr. Goff will present recommendations from a joint NIMH/FDA meeting that focused on important design issues in this area. Finally, Dr. Bush will present the results of a survey of industry decision-makers regarding their attitudes toward collaboration with government and academia.

Wednesday, June 2, 2004

UPDATE SESSION I
1:00 p.m. - 2:00 p.m.

Current and Upcoming Approaches to Medically Supervised Withdrawal from Opioids

Andrew J. Saxon, M.D.
University of Washington

Increasing numbers of individuals are developing dependence on heroin or prescribed opioids. Many of these individuals require and/or request medically supervised withdrawal. This presentation will describe some of the underlying neurobiology and physiology of opioid withdrawal and go on to discuss pharmacologic management of this condition. For the past quarter century the centrally acting alpha-2 adrenergic agonist, clonidine, has been the primary agent used for this purpose. Ultra rapid withdrawal under anesthesia has also been used, but this technique is expensive, requires considerable equipment and expertise and raises safety concerns. In October 2002 the FDA approved the mu-opioid partial agonist, buprenorphine, for the treatment of opioid dependence, although buprenorphine remains unique among pharmaceuticals in that only specially qualified practitioners are permitted to prescribe it. The distinctive pharmacology of buprenorphine will be covered. Data will be presented from an emerging literature suggesting that buprenorphine has superb efficacy and is superior to clonidine in treating opioid withdrawal. Other possible agents for management of opioid withdrawal will be mentioned including lofexidine, an alpha adrenergic agonist that appears to have fewer adverse cardiovascular effects than does clonidine.

Educational Objectives:

1. Understand the physiology and neurobiology of opioid withdrawal.
2. Learn various approaches to pharmacologic management of opioid withdrawal.
3. Learn about the pharmacologic advantages of buprenorphine, a mu-opioid partial agonist recently approved for the treatment of opioid dependence.

UPDATE SESSION I (continued)
1:00 p.m. - 2:00 p.m.

John W. Winkelman, M.D., Ph.D.
Brigham and Women's Hospital

Recent evidence suggests that insomnia has effects well beyond a reduction in sleep time, but rather may have immediate and longstanding effects on quality of life, susceptibility to psychiatric and medical illness, and professional and social functioning. Given these varied burdens of chronic insomnia, it is important to look beyond simple subjective and objective measures of sleep itself to all aspects of treatment efficacy. While existing endpoints used to evaluate the efficacy of insomnia treatment utilize polysomnographic and patient reported measures of sleep onset and sleep maintenance, most studies do not evaluate or report measures of next-day functioning, quality of life outcomes, or effects on co-morbid conditions. We will discuss the importance of these determinants of efficacy, and discuss future directions in evaluating the impact of effective insomnia treatment.

PANEL 1
Acute and Maintenance Treatment of Bipolar Depression: Focus on Rapidly Evolving Methodology
2:15 p.m. - 4:05 p.m.

Efficacy of Lithium Treatment for Depression and Lowering of Suicidal Risk

Leonardo Tondo, M. D.
Università of Cagliari, Italy and Harvard Medical School-McLean Hospital
Carmen Ghiani

Studies reporting on the association of lithium treatment and suicide in bipolar and other major affective disorder patients have consistently found lower rates of suicides and attempts during lithium maintenance treatment than without it.[1-7] Long-term lithium treatment has been associated with a reduction of suicide risk by 85% in a meta-analysis of 22 studies involving a total of 5,647 patients and 33,473 patient-years of risk.[5] In 360 bipolar I and II patients evaluated before, during, and following discontinuation of maintenance lithium treatment, rates of suicide and life-threatening attempts were reduced 6.40 times (83.4%).[8] This reduction was similar to the reduction of suicidal risk in the above-mentioned meta-analysis. Important risk factors were depressive or mixed-dysphoric states, severe previous depressions, and prior suicide attempts. The suicide preventing action of lithium is likely to be associated with the reduction of risk or severity of recurrences in depression or mixed dysphoric-agitated states, [9] although some experts have suggested a specific effect against suicide independent of its mood-stabilizing actions [10].

PANEL 1 (continued)
Acute and Maintenance Treatment of Bipolar Depression: Focus on Rapidly Evolving Methodology
2:15 p.m. - 4:05 p.m.

A similar reduction of suicide risk has not been paralleled by long-term treatment with anticonvulsants. A recent study based on more than 20,000 HMO BP-I patients (1992-2001) showed a 3.2-fold higher risk of suicide in patients treated with anticonvulsants (mainly valproate) compared to lithium-treated patients. The difference in suicidal behavior between the lithium exposed and the depakote exposed was stable over time and was significant for each year individually [11]. This specific value of lithium treatment may include reduction of impulsive, aggressive, or hostile behavior, possibly mediated through the central serotonin system. [12] Inconsistent with this hypothesis is the lack of evidence that serotonin reuptake inhibitor antidepressants have a beneficial effect on suicidality,[13] and that the central antiserotonergic agent clozapine may reduce suicide risk in schizophrenia.[14]

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5. Tondo L et al: Reduced suicide risk with long-term lithium treatment in major affective illness: A meta-analysis. Acta Psychiatr Scand 2001; 104: 163-72
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7. Schou M. Perspectives on lithium treatment of bipolar disorder: action, efficacy, effect on suicidal behavior. Bipolar Disord 1999;1: 5-10
8. Tondo L et al. Lithium treatment and risk of suicidal behavior in bipolar disorder patients. J Clin Psychiatry 1998; 59: 405-14
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10. Müller-Oerlinghausen B. Arguments for the specificity of the antisuicidal effect of lithium. Eur Arch Psychiatry Clin Neurosci 2001;251 (Suppl 2):72-75
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13. Khan A et al. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: An analysis of the FDA database. Arch Gen Psychiatry 2000; 57: 311-17
14. Meltzer HY et al. Reducing suicide risk in schizophrenia: Focus on the role of clozapine. CNS Drugs 2000; 14: 355-65.

PANEL 1 (continued)
Acute and Maintenance Treatment of Bipolar Depression: Focus on Rapidly Evolving Methodology
2:15 p.m. - 4:05 p.m.

Lithium, Divalproex, and Lamotrigine in the Acute and Long-Term Treatment of Bipolar Depression

Joseph R. Calabrese, M.D.
Case Western Reserve University School of Medicine
Melvin D. Shelton, M.D., Ph.D.
Case Western Reserve University School of Medicine

In a small study of patients recently hospitalized for bipolar I depression, Prien et al reported significant evidence of lithium's prophylactic antidepressant efficacy (lithium n=18, placebo n=13; depressive relapses: 12% vs. 55%) in 1973; however, other long-term studies of lithium have limited enrollment to recently manic patients. In a cohort of recently manic patients, Gyulai et al (2003) recently reported the first randomized data to support the long-term efficacy of divalproex in bipolar I depression; a significantly lower percentage of divalproex-treated (6.4%, n=187) than placebo-treated (16.0%, n=94) patients discontinued due to depression. To test the hypothesis that rapid cycling was a predictor of non-response to long-term lithium, an NIMH-funded, 20-month double-blind comparison of lithium monotherapy (n=32) to divalproex monotherapy (n=28) was conducted in a cohort of patients with rapid cycling bipolar disorder. This study was powered to have an 80% chance of uncovering a difference of 20% in overall relapse rates. There were no significant differences in time to treatment for relapse into a mood episode (56% vs. 50%), relapse into depression (34% vs. 29%), or time to relapse into hypomania or mania (22% vs. 22%). All corresponding time to relapse data revealed no significant differences as well. Median survival non-significantly favored divalproex over lithium (45 vs. 18 weeks). However, of those patients not randomized during the open stabilization phase of this study due to lack of efficacy, 75% experienced treatment-refractory depression and were therefore excluded from the randomized pool of monotherapy-treated patients. Overall, the findings from this first long-term comparison of two active treatments for rapid cycling suggest the study's original hypothesis was not supported. To test the hypothesis that lamotrigine was more effective than placebo in preventing relapse in a cohort of recently depressed outpatients with bipolar I disorder, an 18-month multi-center study was conducted across 70 sites and 15 countries (Calabrese et al 2003). In the primary outcome measure, which was time to intervention for treatment of a mood episode, both lamotrigine (n=165) and lithium (n=120) (which was used to gauge study reliability) showed significant improvement over placebo (n=119). In planned secondary analyses, lamotrigine (but not lithium) significantly delayed time to relapse into depression, and lithium (but not lamotrigine) significantly delayed time to relapse into mania; no significant difference were observed between lithium and lamotrigine in all secondary analyses. In a planned meta-analysis of the above lamotrigine study, pooled with a similarly designed studied in recently manic patients, similar findings were observed with the exception that lamotrigine now showed significant improvement over placebo time to relapse into mania, lithium now showed significant improvement over lamotrigine in time to mania, and lithium exhibited a trend (p=0.120) towards improvement in time to relapse into depression. These findings suggest lithium, divalproex, and lamotrigine have a role in the treatment of bipolar disorder, and that properly powered, combination therapy designs need to be conducted to evaluate their combined safety and efficacy.

PANEL 1 (continued)
Acute and Maintenance Treatment of Bipolar Depression: Focus on Rapidly Evolving Methodology
2:15 p.m. - 4:05 p.m.

Olanzapine and Olanzapine-Fluoxetine Combination in the Treatment of Bipolar Depression

Mauricio Tohen, M.D., Dr.P.H.
Lilly Research Laboratories and Harvard Medical School
Eduard Vieta, M.D., Ph.D., Terrence Ketter, M.D., Franca Centorino, M.D.
Joseph Calabrese, M.D., Gary Sachs, M.D., Charles Bowden, M.D., Philip Mitchel, M.D., Richard Risser, M.S., Robert W. Baker, M.D., Angela R. Evans, Ph.D.

Background: Determine the efficacy and safety of olanzapine compared to placebo in the treatment of bipolar depression.

Methods: Patients with bipolar depression and baseline MADRS rating 20 were randomized for eight weeks of double-blind treatment with olanzapine (5-20 mg/d, n=370) or placebo (n=377). Additionally, 86 patients were randomized to the combination of olanzapine (6 or 12 mg/d) plus fluoxetine (25 or 50 mg/d).

Results: Starting at week 1 and sustained throughout the study, improvement for both olanzapine and olanzapine + fluoxetine groups was superior to the placebo group. Endpoint mean MADRS change was significantly greater on olanzapine (-12.7) or olanzapine + fluoxetine (-17.1) than on placebo (-9.4, p<.001). Improvement on olanzapine + fluoxetine was significantly greater than on olanzapine alone (p=.002). Induction of mania (baseline YMRS < 15 and > 15 anytime subsequently) did not differ between groups (olanzapine 5.7%, placebo 6.7%, olanzapine + fluoxetine 6.4%). In the subgroup of patients with a rapid cycling course, olanzapine + fluoxetine was significantly more efficacious than olanzapine and placebo. Common (>10%) and significant adverse events reported in the olanzapine group compared to placebo were somnolence, weight gain, increased appetite, and dry mouth, whereas headache and insomnia were more common and significant on placebo.

Conclusion: Olanzapine demonstrated superiority to placebo in the treatment of bipolar depression; olanzapine + fluoxetine also showed superiority compared to placebo and to olanzapine.

PANEL 2
Advances in Geriatric Psychopharmacology
2:15 p.m. - 3:45 p.m.

Overview

This symposium highlights four topics of major current concern in geriatric psychopharmacology. In the first paper Lon Schneider will use experience in the CATIE Alzheimer disease trial to discuss the process by which new information is evaluated and incorporated into an active protocol. In the second paper Eric Lenze will describe his current work on genetic factors in the incidence of depression and late life and describe an approach to incorporation of genetic factors into clinical trials. Martha Bruce will describe the suicide risk management approach developed for use in a large trial of depression in primary care and will discuss general principles for use in trials with fragile patients. In the final paper, Laura Dunn will describe experimental approaches to methods of enhancing capacity and on the process of obtaining informed consent for research in patients with cognitive impairments.

Gene-Environment Interactions in Late Life Mental Disorders

Eric Lenze, M.D.
Western Psychiatric Institute and Clinic

Recent findings suggest an interaction between specific candidate genes and the environment for the onset of depression. Dr. Lenze will describe the current knowledge about candidate genes which are believed to be involved in the onset or maintenance of depression and other late-life mental disorders. He will review the literature regarding genetic prediction of onset of depression in elderly persons. He will also present preliminary data demonstrating that serotonin transporter polymorphism interactions with severe medical stress are predictive of onset of depression in a sample of elderly persons who suffered a hip fracture. Such results have implications for the prediction of risk for depression in medically ill and disabled elderly. Along with these preliminary findings, Dr. Lenze will describe potential approaches for incorporating genotyping in clinical trials, including prevention trials, for late-life depression and anxiety disorders.

Educational Objectives:

1. Understand how specific candidate genes could affect the onset and course of late-life depression.
2. Understand how genotyping could be potentially used to identify high-risk patients for clinical trials of preventive interventions.
3. Understand how genotyping could be used to identify in advance poor responders to treatment in clinical trials.

Wednesday, June 2, 2004 (continued)

PANEL 2 (continued)
Advances in Geriatric Psychopharmacology
2:15 p.m. - 3:45 p.m.

Enhancing the Capacity to Consent in Geriatric Trials

Laura B. Dunn, M.D.
University of California, San Diego

This presentation will review the literature on methods of improving the consent process for research in older people. Multiple potential barriers to informed consent confront geriatric psychiatry investigators who wish to conduct research into a variety of disorders. By categorizing these potential barriers into several categories (participant-related, consent-related, and investigator-related), they may be addressed directly, thereby optimizing the consent process. Participant-related factors include age, education, cognitive impairment, decision-making capacity, prior research experience, and emotional variables. Participants at risk for impaired decision-making capacity should be assessed using methods specific to this task. On the other hand, a psychiatric diagnosis per se does not imply impaired decision capacity. Problems with understanding of consent may, in fact, relate back to the consent form or method itself. Consent-related factors include writing or presentation style, technology, reading level, length, and complexity of the consent. Efforts to address some of these variables have met with some success but research is still in its infancy, especially in geriatric psychiatry populations. Investigator-related factors include attitudes toward and interest in informed consent, training in administration or enhancement of informed consent, time pressures, and staff mastery of new techniques. Each of these three categories of barriers can be examined by investigators and addressed using relatively simple techniques.

Learning Objectives:

1. Identify categories of potential barriers to informed consent in clinical trials involving older individuals with a variety of illnesses.
2. Review findings on methods of enhancing the consent process in order to break down potential barriers to consent.
3. Discuss possible approaches to optimizing informed consent in individuals with cognitive impairment.

TREATMENT DEVELOPMENT SESSION 3
Neuroplasticity and Cellular Resilience - Translational Research
2:15 p.m. - 4:15 p.m.

Overview

There is mounting evidence that recurrent mood disorders - once considered "good prognosis diseases" - are, in fact, often very severe and life-threatening illnesses. Recurrent mood disorders can have devastating long-term effects, and the cost of these illnesses in terms of human suffering, productivity and health care is enormous. Suicide is the cause of death in 10-20% of individuals, and in addition to suicide, mood disorders are associated with many other deleterious health-related effects. Not surprisingly, the costs associated with disability and premature death represents an economic burden of tens of billions of dollars annually in the United States alone. It is now recognized that, for many patients, the long-term outcome is often much less favorable than previously thought, with incomplete interepisode recovery, and a progressive decline in overall functioning observed. Indeed, according to the Global Burden of Disease Study, mood disorders are among the leading causes of disability worldwide, and are likely to represent an increasingly greater health, societal, and economic problem in the coming years. Despite the devastating impact that these diseases have on the lives of millions worldwide, there is still a dearth of knowledge concerning their underlying etiology and pathophysiology. There is thus considerable excitement regarding recent cellular and molecular biological studies, which have identified critical molecules regulating signaling and cellular plasticty and resilience as playing critical roles in the pathogenesis and treatment of severe mood disorders. This panel will bring together a group of leading preclinical and clinical investigators to bring their expertise to bear upon the questions pertaining to the role of cellular plasticity and resilience in severe mood disorders. Harold Sackeim, PhD (Columbia University) will open with a state of the art discussion pertaining to the Neuroimaging and Cognitive Deficits in severe mood disorders. He will discuss the recent morphometric studies of the brain (both in vivo and postmortem) that are leading to a fuller appreciation of the magnitude and nature of the neuroplastic events involved in the pathophysiology of mood disorders. This work – arising from recent clinical and preclinical studies using diverse paradigms – suggest that a reconceptualization about the pathophysiology, course, and optimal long-term treatment of recurrent mood disorders may be warranted. He will further discuss the Neuropsychological assessments of euthymic bipolar patients that suggest that deficits persist during remission. Furthermore, a few recent studies provide evidence of selective neuropsychological deficits in high-risk groups in bipolar disorder. The neural correlates inferred from neuropsycholo gical studies are consistent with reports from functional neuroimaging and neuropathological studies which have identified prefrontal cortex disturbance and disruption of frontostriatal circuits in severe mood disorders. Next, Philip Haydon, PhD (University of Pennsylvania) will follow with a discussion of the tremendous recent progress in our understanding of the critical roles of glial cells in regulating neuronal function. Thus, there is now compelling evidence that radial glial cells have the potential to self-renew and to generate both neurons and astrocytes. Glial cells play critical roles in regulating synaptic glutamate levels, CNS energy homeostasis, liberation of trophic factors, increase the number of mature, functional synapses on CNS neurons, and indeed form dynamic, complex synaptic networks with neurons. Finally, Dr. Husseini K. Manji, MMD (NIMH) will discuss the recent genomic and proteomic studies that have led to the identification of neurotrophic signaling cascades as targets for mood-stabilizers. These studies have shown that critical molecules in neurotrophic signaling cascades (CREB, BDNF, bcl-2, GSK-3, MAP kinases) are long-term targets for mood-stabilizers. Consistent with these biochemical effects, mood-stabilizers (most notably lithium) have been demonstrated to exert robust neuroprotective and neurotrophic effects in a variety of preclinical paradigms. Complementary human studies have shown that chronic lithium significantly increases gray matter content in a reginally selective manner, suggesting a reversal of illness-related atrophy and an increase in the volume of the neuropil. The growing body of preclinical/clinical data suggests that for many refractory patients, new drugs simply mimicking many “traditional” drugs which directly or indirectly alter neurotransmitter levels and those which bind to cell surface receptors may be of limited benefit. For these patients, optimal treatment may only be attained by providing both trophic and neurochemical support; the trophic support would be envisioned as enhancing and maintaining normal synaptic connectivity, thereby allowing the chemical signal to reinstate the optimal functioning of critical circuits necessary for normal affective functioning. There are a number of pharmacologic "plasticity enhancing" strategies being investigated which may be of considerable utility in the treatment of mood disorders; this research hold much promise for the development of novel therapeutics for the treatment of bipolar disorder.

PANEL 3
Current Status and Controversies in Antipsychotic Drug Effectiveness: Update from the CATIE Study
4:00 p.m. - 5:45 p.m.

Overview

The Clinical Antipsychotic Trials of Intervention Effectiveness project (CATIE) is a National Institute of Mental Health-sponsored research project to evaluate the clinical effectiveness of atypical antipsychotics in the treatment of schizophrenia and Alzheimer's disease. Although they were first developed for schizophrenia, antipsychotic drugs are now broadly used for other disorders, including behavioral signs and symptoms associated with Alzheimer's disease. Despite their widespread use in these conditions, the overall effectiveness and safety of these drugs remain unclear.

In recent years clinical psychopharmacology research has been dominated by the pharmaceutical industry. While industry-sponsored research is critical to new product development, its emphasis is on meeting regulatory and marketing requirements rather than the effectiveness of the drugs at the general population level. As a result, industry-sponsored research does not address broad public health needs or the needs of individual practitioners seeking to make good clinical decisions for individual patients.

The CATIE trials are examples of practical clinical trials–they are meant to produce results that are generalizable to typical treatment settings and to generate information that is useful to clinical and policy decision-makers. The trials have been underway since 2001 and will be complete by the end of 2004. Information on the safety and effectiveness of the drugs that have become available since the trails began has only increased the importance of the two CATIE trials.

- Large Practical Clinical Trials: rationale and design issues–Robert Rosenheck, MD
- Metabolic syndrome and antipsychotic drugs: risks and considerations-Don Goff, MD
- Antipsychotic drug treatment of AD: update on the CATIE trial–Lon Schneider, MD
- Antipsychotic drug treatment of schizophrenia: update on the CATIE trial–Scott Stroup, MD

Efficacy vs. Effectiveness of Second Generation Antipsychotics: Is Haloperidol Without Prophylactic Anticholinergics a Fair Comparitor?

Robert Rosenheck, M.D.
Yale University School of Medicine

Two-thirds of clinical trials of second generation antipsychotics (SGAs) for schizophrenia have used haloperidol without prophylactic anticholinergics as the comparator. A recent multi-site VA trial suggested that when haloperidol is given with prophylactic benztropine, olanzapine showed no advantage for either positive or negative symptoms. Past research shows that without prophylactic anticholinergics 19%-30% of patients treated with SGAs develop akinesia with inactivity, social withdrawal, and depression, but without Parkinsonian symptoms, indistinguishably mimicking negative symptoms of schizophrenia. Under-treatment of akinesia among haloperidol patients may also explain why benefits for negative symptoms and depression appear to be greater than benefits for positive symptoms in the many SGA trials that did not use prophylactic anticholinergics. In addition, a review of recent meta-analyses shows that, although few in number, studies that used haloperidol with prophylactic anticholinergics were substantially less likely to show significant clinical benefits from SGAs than those that did not use such prophylaxis. Since failure to use prophylactic anticholinergic medication with haloperidol may have biased many randomized clinical trials and meta-analyses that demonstrate greater efficacy of SGAs as compared to FGAs, there is a need for studies that avoid this bias. The NIMH-funded CATIE trial is perhaps that last best hope for fairly addressing this issue.

PANEL 3 (continued)
Current Status and Controversies in Antipsychotic Drug Effectiveness: Update from the CATIE Study
4:00 p.m. - 5:45 p.m.

Metabolic Syndrome and Antipsychotic Drugs: Risks and Considerations

Donald C. Goff, M.D.
Massachusetts General Hospital/Harvard Medical School

Metabolic syndrome is defined as the presence of at least three of the following five factors: abdominal adiposity as determined by waist circumference, hypertension, elevated triglycerides, low HDL cholesterol, and insulin resistance as determined by a fasting blood sugar. The steadily increasing prevalence of metabolic syndrome over the past few decades in the United States is of great concern because of the strong links to diabetes, cardiovascular disease and mortality. Metabolic syndrome in individuals with chronic mental illness has recently become the subject of study and debate, as some evidence suggests an elevated prevalence, prior to initiation of treatment, in first episode patients with schizophrenia and an increased risk for metabolic syndrome associated with some atypical antipsychotics. The CATIE study will allow us to examine the prevalence of metabolic syndrome at baseline in a large representative sample of chronic schizophrenia patients and the impact of an 18 month exposure to atypical antipsychotics.

Antipsychotic Drug Treatment of Schizophrenia: Update on the CATIE Trial

Scott Stroup, M.D., M.P.H.
University of North Carolina at Chapel Hill

The CATIE schizophrenia trial, a practical trial intended to evaluate the effectiveness of antipsychotic drugs, ended enrollment in June 2003 with 1493 individuals randomized to double-blinded treatment with olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone in the initial phase of the study. An initial goal of the study was to enroll a sample representative of individuals with schizophrenia receiving treatment in typical clinical settings. The randomized subjects included 1101 (76%) men and 392 (24%) women. Fifty-nine percent of subjects were white, 36% were African-American or black, 2% were Asian, and 2% reported more than one race. Less than 1% of subjects were Pacific Islanders or Native Americans. Twelve percent were Hispanic. Most subjects had not been hospitalized or required crisis services in the three months prior to study entry–only 27% had used these services. At baseline, 42% of subjects were obese, 37% met criteria for hypertension, 64% met criteria for dyslipidemia, and 12% had evidence of diabetes mellitus. Thirty-four percent of subjects were users of illicit substances. Only 15% of subjects were employed. Results of the trial are expected in 2005.

Wednesday, June 2, 2004 (continued)

PANEL 4
The Anxiety Spectrum and Its Emerging Treatments
4:00 p.m. - 5:45 p.m.

Overview

Learning Objectives: Upon the completion of this symposium, participants will be able to:

- Recognize the complexities and challenges in the diagnosis and treatment of anxiety disorders, both comorbid and not comorbid with depression.
- Gain and improve knowledge about emerging new treatments for the anxiety disorders, including obsessive compulsive disorder, post traumatic stress, and related disorders, such as body dysmorphic disorder.

Anxiety disorders are among the most common psychiatric illnesses to affect children and adults. Although highly treatable, only about one-third of those who suffer from an anxiety disorder receive appropriate treatment. Furthermore, a significant proportion of patients are either intolerant or poorly responsive to standard treatment.

Numerous studies have shown that psychosocial therapies, medications, or both used in combination, can successfully treat anxiety and related spectrum disorders, including body dysmorphic disorder. However, efficacy and side effect concerns with respect to available treatments have given rise to the growth of new approaches, including acupuncture, brief therapy and deep brain stimulation.

This panel will explore the epidemiology, psychobiology, and treatment of anxiety disorders and body dysmorphic disorder, with a focus on conceptualization and new treatment strategies.

Anxiety and Comorbid Major Depression

Philip T. Ninan, M.D.
Emory University School of Medicine

Learning Objectives: Upon the completion of this symposium presentation, participants will be able to

- Describe the epidemiology, neurobiology, and pathophysiology of anxiety disorders and comorbid major depression.
- understand the potential mechanisms of treatment response of medications and psychotherapies for anxiety and depression.

Anxiety and depressive disorders are highly prevalent and comorbid. Treatments can be beneficially unique to each of these syndromes, or overlap in their efficacy. How can we explain the complex relationship and derive guidelines for treatment? Phenomenology has had only partial success in answering such questions. Can neurobiology enlighten us?

Preclinical and clinical studies suggest the experience of anxiety is mediated by neural circuits with the extended amygdala as a central hub. Pathological experiences of anxiety include the conditioning of fear responses through the amygdala. Contextual conditioning may involve the hippocampus leading to anticipatory anxiety. Avoidance conditioning appears to involve the medial prefrontal circuits and their interaction with the amygdala. The circuits that are implicated in major depression are similar, and may include dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis.

The mechanism of treatment response can be examined in an exploratory and explanatory manner. Pharmacologically, 'bottom-up' manipulation of serotonin and norepinephrine results in remission of anxiety and depressive disorders in a proportion of patients, though other neurotransmitters, neuropeptides and neurotrophic factors also have a substantial role. The therapeutic benefit of cognitive-behavioral therapy is postulated to have a 'top-down' influence on neural circuits by providing a cognitive context to alter the activity of lower centers. Understanding the mechanism of action of different treatments will allow the prescription of treatments based on the specific benefits required.

PANEL 4 (continued)
The Anxiety Spectrum and Its Emerging Treatments
4:00 p.m. - 5:45 p.m.

Deep Brain Stimulation for Intractable OCD

Wayne K. Goodman, M.D.
University of Florida

Learning Objectives: Upon the completion of this symposium presentation, participants will be able to

- Describe the rationale for neurosurgery in the treatment of refractory OCD.
- Discuss the vast differences between past and present neurosurgical approaches.
- Describe Deep Brain Stimulation and its potential use for intractable OCD.

Obsessive-compulsive disorder (OCD) is defined as a condition in which a person has repeated and uncontrollable thoughts (obsessions) that are accompanied by persistent urges to perform repetitive rituals (compulsions). OCD has a chronic course, and few patients achieve true remission. The treatment of severe or intractable OCD is a major challenge in psychiatry. Recently, the utilization of non-pharmacological biological interventions, such as Deep Brain Stimulation (DBS), is being studied in the treatment of refractory OCD. Pathophysiological models of OCD suggest a dysfunction of cortico-striato-thalamocortical (CSTC) circuits in the brain. High frequency subthalamic stimulation, such as DBS, in patients with Parkinson's disease has proven efficacy, and initial data for DBS in treatment-resistant OCD are promising.

This presentation will also discuss the rationale for neurosurgery and will review the history of psychosurgery, including prefrontal lobotomy, in the treatment of psychiatric illnesses. DBS will be defined, and the inherent advantages of DBS over previous lesioning procedures will be reviewed. Unlike ablative neurological approaches, DBS is non-destructive and stimulation parameters (e.g., frequency, voltage, electrode configuration, etc.) can be adjusted to optimize treatment response; like ablative approaches, DBS is highly invasive and should be considered only as a last resort option. This presentation will also describe new studies being conducted to evaluate the efficacy and safety of DBS in treatment-resistant OCD.

Wednesday, June 2, 2004 (continued)

PANEL 4 (continued)
The Anxiety Spectrum and Its Emerging Treatments
4:00 p.m. - 5:45 p.m.

Body Dysmorphic Disorder

Katharine A. Phillips, M.D.
Brown University Medical School/Butler Hospital

Learning Objectives: Upon the completion of this symposium presentation, participants will be able to:

- Recognize the clinical features of body dysmorphic disorder.
- Appreciate new clinical approaches to the treatment of BDD and understand recent genetic findings with potential treatment implications.

Body dysmorphic disorder (BDD) is characterized by a preoccupation with an imagined or slight defect in appearance that causes clinically significant distress or impairment in functioning. Although BDD is classified as a somatoform disorder, it has similarities to, and may be related to, the anxiety disorders-in particular, obsessive-compulsive disorder (OCD) and social phobia. BDD is characterized by obsessional preoccupations focusing on the perceived "defect," as well as time-consuming repetitive behaviors. It causes severe impairment in functioning and is associated with unusually poor quality of life.

Treatment research has rapidly increased in recent years, with emerging data consistently indicating that serotonin reuptake inhibitors (SRIs) are often efficacious for BDD, probably preferentially. Of note, SRIs as monotherapy appear efficacious for patients with delusional BDD (as well as patients with nondelusional BDD). Although data are limited, it appears that higher SRI doses and longer treatment trials than those used for many other psychiatric disorders are often needed to effectively treat BDD, and that relapse rates are very high with SRI discontinuation. Unlike findings in OCD, a recent preliminary study of pimozide augmentation of fluoxetine found that pimozide was not more efficacious than placebo. Preliminary findings also suggest that cognitive-behavioral therapy is often efficacious for BDD. However, treatment data (both psychosocial and psychopharmacologic) remain very limited, and additional research is needed.

This presentation will present recent data on BDD's clinical features and treatment response, as well as data from a preliminary genetics study which found an association for the GABAA- 2 (5q31.1-q33.2) gene (p=.012) and for the 5-HTTLPR (17q11.1-q12) gene at a trend level (p=.064), with the s/s genotype more common in BDD subjects than in matched healthy controls. These results are consistent with the efficacy of SRIs for BDD and suggest a possible role for GABAergic medications in treating BDD, which have not been studied in this disorder.

PANEL 4 (continued)
The Anxiety Spectrum and Its Emerging Treatments
4:00 p.m. - 5:45 p.m.

Acupuncture and CBT Treatment of PTSD

Michael Hollifield, M.D.
University of New Mexico

Learning Objectives: Upon completion of this symposium presentation, participants will be better able to:

- Discuss and compare the novel therapies used for the treatment of PTSD.
- Describe the scientific rationale for the use of acupuncture in PTSD treatment.
- Review the recent clinical trials of acupuncture.
- Understand its integration into the clinical setting.

Posttraumatic stress disorder (PTSD) arises following exposure to events that are perceived as a threat to one's life or integrity. Frequent nightmares and sleep impairment are often reported in PTSD. Effective therapies for PTSD consist of pharmacologic interventions, such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and benzodiazepines, as well as non-pharmacologic interventions (i.e., psychotherapy). Cognitive behavioral therapy (CBT) or cognitive re-structuring shortly after acute stress reduce the risk for developing PTSD. CBT studies using desensitization and imagery rehearsal therapy (IRT) have demonstrated large reductions in nightmares and other symptoms of PTSD.

More recent studies using acupuncture for alleviating symptoms associated with anxiety, depression, pain, and insomnia suggest that this form of therapy may be effective for PTSD. Evidence from experimental and clinical studies suggests that acupuncture exerts an influence on the endogenous opioid system, which may also affect autonomic nervous system functions. Other possible mechanisms of action of acupuncture treatment for PTSD also will be discussed. Our recent clinical trial designed to compare acupuncture to CBT (to a wait-list control) for the treatment of PTSD will be discussed, and Traditional Chinese Medicine diagnostic data for PTSD will be presented.

Can Pharmacotherapy Prevent PTSD?

Jonathan Davidson, M.D.
Duke University Medical Center

Learning Objective:

- Upon the completion of this symposium presentation, participants will be able to have an increased under standing of the pharmacotherapy used to prevent the development of posttraumatic stress disorder.

Posttraumatic stress disorder (PTSD) is a chronic, disabling, and sometimes debilitating consequence of exposure to trauma. It is often complicated by the fact that it frequently occurs in conjunction with other psychiatric comorbidities, such as depression, substance abuse, or other anxiety disorders. The net effect of PTSD is a significantly impaired quality of life, including occupational instability and excessive hospitalization, which creates a significant social and economic burden for patients, families, and society as a whole. Therefore, early diagnosis and intervention of PTSD are the keys to preventing the development of acute stress symptoms and the late-onset symptoms of established PTSD. Current pharmacotherapies to prevent the development of PTSD will be reviewed, which include the use of corticosteroids, imipramine, and high-potency benzodiazepines. This talk will focus on the emerging evidence for the role of drugs in the immediate aftermath of exposure to trauma.

TREATMENT DEVELOPMENT SESSION 4
New Concepts in the Pathophysiology and Treatment of Mood Disorders
4:15 p.m. - 6:00 p.m.

The Role of Signaling Cascades on Neuroplasticity: Relevance to the Pathophysiology of Mood Disorders.

Husseini K. Manji, M.D.
National Institute of Mental Health

Severe mood disorders, traditionally conceptualized as neurochemical disorders, are in fact additionally associated with impairments of structural plasticity and cellular resilience. It is thus noteworthy that recent preclinical studies have shown that critical molecules in neurotrophic signaling cascades are long-term targets for antidepressant agents and antidepressant potentiating modalities. Therefore, therapeutics designed to enhance cellular plasticity and resilience and that counter maladaptive stress-responsive systems may have considerable utility for the treatment of mood disorders. Effective treatments should provide both trophic and neurochemical support, which serves to enhance and maintain normal synaptic connectivity, thereby allowing the chemical signal to reinstate the optimal functioning of critical circuits necessary for normal affective functioning. Newer "plasticity enhancing" strategies that may have utility in the treatment of mood disorders include the modulation of the glutamatergic complex of receptors, modulation of protein kinase cascades (PKA, PKC), and modulation of the hypothalamus-pituitary-adrenal axis (glucocorticoid's system activity). Finally, the study of the mechanism of action of newer effective molecules, antipsychotic and antiepileptic drugs, is also contributing to the task of unveiling the pathophysiology of mood disorder to develop novel and improved medications. While this task is truly daunting, these, and similar approaches, will ultimately lead to better medications for the millions who suffer from this devastating illness.

Learning Objectives:
1. To understand the role of signaling cascades on neuroplasticity.
2. To understand the role that newer "plasticity enhancing" strategies may have in the treatment of mood disorders.

Protein Kinase C Activation Impairs Prefrontal Cortical Function: Relevance to Neuropsychiatry

Amy F.T. Arnsten, Ph.D.
Yale University School of Medicine

The prefrontal cortex (PFC) is essential for regulating behavior, thought and affect using working memory. PFC dysfunction has been characterized in schizophrenia, major depressive disorder and bipolar disorder. Studies in animals and humans have shown that exposure to uncontrollable stress markedly impairs PFC function, and stress can worsen the symptoms of many neuropsychiatric disorders. Intensive studies in animals have shown that stress impairs PFC function via release of high levels of catecholamines, which engage dopamine D1 receptors activating protein kinase A, and norepinephrine alpha-1 receptors activating protein kinase C. These findings are substantially different from those found in posterior cortex and subcortical structures. The unique chemical needs of the PFC must be kept in mind when designing pharmacological therapies for neuropsychiatric disorders.

Learning Objectives:
1. To understand the role of the prefrontal cortex in guiding behavior, thought and affect, and the disruption of its function during stress and in neuropsychiatric illness.
2. To understand the detrimental effects of protein kinase A signaling on prefrontal cortical cognitive function.
3. To understand the detrimental effects of protein kinase C signaling on prefrontal cortical cognitive function.

TREATMENT DEVELOPMENT SESSION 4 (continued)
New Concepts in the Pathophysiology and Treatment of Mood Disorders
4:15 p.m. - 6:00 p.m.

Modulation of Glutamatergic and Dopaminergic Activity in Patients with Mood Disorders: Results from Recent Clinical Trials

Carlos A. Zarate, Jr., M.D.
National Institute of Mental Health

There is a growing appreciation that for many refractory patients, new drugs that directly or indirectly only alter monoamine levels may be of limited benefit. In this context, there is a growing body of data suggesting that modulation of the glutamatergic system (which is known to play a major role in neuronal plasticity and cellular resilience) and modulation the dopaminergic system by pramipexole (a D3 agonist that has neurotrophic properties) may be involved in the pathophysiology and treatment of mood disorders. Recent preclinical studies have shown that the glutamatergic system represents targets for the actions of antidepressants and mood stabilizers. Interestingly, there are a number of glutamatergic "plasticity enhancing" strategies which may be of considerable utility in the treatment of mood disorders. Similarly, pramipexole as a "plasticity enhancing" agent may also have antidepressant properties in unipolar and bipolar patients. Safety and efficacy data from recent and ongoing clinical trials, conducted at the NIH Intramural Research Program, with drugs that modulate the glutamatergic and dopaminergic activity are discussed. This research progress holds much promise for the development of novel therapeutics for the treatment of severe mood disorders.

Learning Objectives:

1. To understand the extent of the glutamatergic system's involvement in the pathophysiology of mood disorders.
2. To understand the role that glutamatergic modulators may have as a novel therapeutic interventions for the treatment of mood disorders.
3. To understand the role that the dopaminergic agonist pramipexole may have as a novel therapeutic intervention for the treatment of bipolar disorder.

Recent Studies on Mifepristone, a Glucocorticoid Antagonist, in Psychotic Major Depression

Alan D. Schatzberg, M.D., Benjamin Flores, M.D., Brent Solvason, M.D., Ph.D., Heather Kenna, Jennifer Keller, M.D.
Stanford University

Psychotic major depression is a relatively common subtype of depression. It is characterized by excessive activity of the hypothalamic-pituitary-adrenal (HPA) axis activity. Previous reports have pointed to possible benefit of acute treatment with mifepristone, a glucocorticoid receptor antagonist, in patients with the disorder.

We present recent data from a study that included PMD 30 patients, 30 non-psychotic major depressives and 30 healthy controls. HPA axis activity from 1800 hr. to 0900 hr. was assessed, as were neuropsychological testing and structural and functional MRI. PMD patients demonstrated significantly elevated cortisol levels between 1800 hr. and 0400 hr., the expected quiescent period. In addition, PMD patients demonstrated significant impairment in executive function and verbal memory in comparison to the other 2 groups.

PMD patients were randomized to 8 days of treatment with mifepristone or placebo under double-blind conditions. Mifepristone produced significantly greater improvement in positive (psychotic) symptoms, as measured using the BPRS positive symptom scale, than did the other groups. Data on changes in cortisol levels and rhythm on drug vs. placebo point to possible mechanisms that may underlie the suggested enduring effects of therapy.

Educational Objectives:

1. Provide an update on the biology and clinical morphology of psychotic major depression.
2. Review recent data on mifepristone in the treatment of the disorder.

Thursday, June 3, 2004

PANEL 5
Abuse Liability Assessment: Getting the Right Data at the Right Time
8:30 a.m. - 10:30 a.m.

Abuse Liability Assessment and Drug Dependence: Scientific and Regulatory Considerations in Drug Development

Deborah B. Leiderman, M.D.
Food and Drug Administration

Summary: This presentation will review the requirements for the characterization of a CNS-active new drug with potential for abuse, under the Federal Food Drug and Cosmetic Act (FFDCA) and under the Controlled Substance Act (CSA). Scheduling of drugs under the CSA and criteria for placement of drugs and substances into each of the five schedules will be discussed. The session will enhance attendees' understanding of regulatory requirements, the Controlled Substances Act, and the scientific and regulatory aspects of abuse risk assessment and drug scheduling.

Learning Objectives:
1. Participants will understand the requirements for the characterization of a new drug's potential for abuse under the FFDCA as well as under the CSA.
2. Participants will be introduced to the process of drug scheduling in the United States; will understand the respective roles of the FDA, DHHS, and the DEA and the criteria for a drug's placement into one of the five schedules of the CSA.
3. Participants will be introduced to the kinds of scientific data which are important for an abuse liability assessment.

New drugs in development whose chemistry, pharmacology, clinical, and/or behavioral effects suggest CNS activity must be assessed for abuse liability.

The Federal Food, Drug and Cosmetic Act (FFDCA) (21 CFR § 314.50 (5) (vii)) requires full characterization of a new drug with potential for abuse. In addition, Investigational New Drugs (INDs)and New Drug Applications (NDAs) for drugs with known or potential abuse liability must meet the requirements of the Controlled Substance Act (CSA) (21 USC 811 (f) and 812). Under the FFDCA, the determination of the abuse potential of a drug is considered to be part of the evaluation of a drug's safety and efficacy. The definition of abuse liability and the general FDA/CDER scientific guidelines and principles of abuse liability assessment will be presented. Abuse liability assessment is based upon multiple kinds and sources of data. Since no single test can definitively characterize a drug or, with absolute certainty predict abuse liability, the abuse liability assessment process constructs a composite "picture" of a drug. All aspects of a drug are considered including its chemistry, pharmacology, pharmacodynamics, pharmacokinetics, preclinical (animal) and human laboratory abuse liability data as well as clinical trial and post-marketing data when available.

Scheduling of drugs under the CSA and criteria for placement of drugs and substances into each of the five schedules will be discussed. The role of CDER within the FDA and DHHS, and with respect to the Drug Enforcement Administration (DEA), in the processes of both domestic and international scheduling actions will be discussed.

PANEL 5 (continued)
Abuse Liability Assessment: Getting the Right Data at the Right Time
8:30 a.m. - 10:30 a.m.

Human Abuse Liability Studies: Design and Interpretation

Edward M. Sellers, M.D., Ph.D.
Ventana Clinical Research Corporation and University of Toronto

Structured abuse liability studies in drug experienced human volunteers are a critical part of the overall evaluation of psychoactive drugs. Such studies have good predictive validity when interpreted in the context of other preclinical and clinical data. Key design features of such studies include: single dose cross over balanced design; pre-study confirmation that drug experienced subjects can reliably identify drug class effect; selection of a drug class appropriate positive control and negative control; no less than 2 doses of active drug; selection of predictive primary dependent variables (e.g. VAS-drug-liking, VAS-high, Cole ARCI euphoria scale; subjective drug price). The maximum selected doses of active drug should be at least 3 times the expected maximum therapeutic dose. Study conduct and electronic data collection should be GCP and 21 CFR II compliant respectively. Examples to illustrate these issues involving stimulants, NMDA antagonists, opioids, atypical antidepressants and other drug classes will be used.

Because human abuse liability studies provide critical information for marketing and business decisions, they should be considered early and included in the overall drug development plan.

Educational Objectives
1. Specify the experimental design for human abuse liability studies.
2. Identify the sources of experimental variation that must be controlled.
3. Understand the contribution of human abuse liability studies to overall assessment of abuse and dependence in an NDA submission.

Thursday, June 3, 2004

PANEL 5 (continued)
Abuse Liability Assessment: Getting the Right Data at the Right Time
8:30 a.m. - 10:30 a.m.

Clinical Trial Data: What is needed?

Joseph M. Frey, Ph.D.
AstraZeneca

Learning Objectives

- To examine sources of clinical data and to recognize critical design elements that can provide signals of potential abuse liability.
- To review the currently available validated instruments that can be practicably embedded into existing clinical trial designs.
- To emphasize the need for further research in this area.

Abuse liability assessment of CNS candidate drugs should be a continuous activity throughout the entire drug development process. Assessment of compounds with novel mechanisms of action begins with observational studies in animals and progresses to specific preclinical studies of self-administration, drug discrimination, tolerance and withdrawal phenomena. If an early signal is detected, dedicated human laboratory studies may be performed against relevant comparators known to exhibit abuse potential. Data from clinical trials aimed at demonstrating safety, tolerability and efficacy of a new candidate drug can also provide early signals of abuse liability and can assist in directing the dedicated investigations of abuse liability later in the development process.

The aim of this panel discussion is to examine approaches to clinical trial design and collection and interpretation of clinical trial data as well as to discuss and critically evaluate the utility of early phase (Phases I and II) and Phase III clinical studies to assess the abuse potential of a drug under development. A survey will be conducted of the various sources of clinical trial data available for this purpose, beginning with standard clinical findings of spontaneous reports, adverse events, non-prescribed patterns of use and extending to specialized embedded measures to assess performance, cognition, mood and drug liking. The impact of the subject population and typical dose ranges employed during Phase I-III trials on the interpretation of data will also be discussed. The presentation will conclude with a brief review of areas and methods in need of future exploration.

Monitoring the Diversion and Non-Medical Use of Psychotropic Drugs

Charles R. Schuster, Ph.D.
Wayne State University School of Medicine

This presentation will describe the major sources of data on prescription drug use, diversion and non-medical use. The limitations of most national surveys for the detection of drug abuse and diversion of specific drugs and drug classes will be discussed. Methods that have been utilized for the post-marketing surveillance of the potential diversion and abuse of several specific drug products will be described. Strengths and limitations of these approaches and the need for further methodological research in this area will be emphasized.

Teaching Goals: Individuals attending this lecture should become acquainted with:

1. The need for post-marketing surveillance as the basis for directing risk management strategies.
2. Sources of information on drug use diversion illegal drug use morbidity and mortality associated with illegal drug use.
3. The strengths and weaknesses of various post-marketing methods for assessing the magnitude and public health consequences of diversion and illegal use of new psychotropic drugs with abuse potential.

PANEL 6
Somatic Treatments for Mental Disorders: Current Status and Future Directions
8:30 a.m. - 11:30 a.m.

Bilateral Grand-Mal Seizures are Essential to Behavioral Benefits in Severe Psychiatric Illnesses

Max Fink, M.D.
SUNY at Stony Brook

Convulsive therapy was conceived in 1928 when Meduna found increased gliosis in the brains of epileptic patients and reduced gliosis in those with dementia praecox. Epidemiologic studies showed a low incidence of psychosis in patients hospitalized for epilepsy and a parallel low incidence of spontaneous seizures in patients with dementia praecox. After animal trials to find a safe seizure inducing agent, Meduna established the safety of intramuscular camphor and demonstrated the efficacy of the treatments in the relief of catatonia. Efforts to improve seizure induction efficacy have been a focus of interest over many decades.

Camphor was replaced by intravenous Metrazol within the first year and by electrically induced seizures in May 1938. Alternative chemical inductions (flurothyl, carbon dioxide, nitrous oxide), subconvulsive procedures (hemi-seizures, electroanesthesia, non-convulsive electrotherapy, unidirectional low voltage frontal lobe stimulation), lidocaine-modified seizures, and isoflurane anesthesia were next tested. Varying frequencies of seizures and ectric current characteristics, electrode placement (unilateral, bitemporal, bifrontal), and energy dosing followed. Lately, interest has shifted to magnetic stimulation instead of electrical, stimulation of vagus nerve and brain stem in modifications labeled TMS, VNS, and DBS, each without seizure induction. Also, seizure induction by high energy magnetic stimulation (MST) has been tested. Only seizures induced by Metrazol, flurothyl, and electricity via bilateral electrode placement have proven reliable and effective.

An induced grand mal seizure is the essential therapeutic event. The mode of induction of seizures is irrelevant. Seizure efficacy is best defined by the ictal EEG and the release of neurohormones into the blood and CSF. The essential question is which brain chemical events that result from induced grand mal seizures are in the therapeutic chain. Dallying with non-seizure methods is opportunism, with little likelihood of replacing convulsive therapy.

Educational Objectives:
1. Understand the role of grand mal seizures in the history of modern convulsive therapy.
2. Appreciate the central nature of grand mal seizures in convulsive therapy.
3. Appreciate why non-seizure methods over half a century have failed.

Thursday, June 3, 2004 (continued)

PANEL 6 (continued)
Somatic Treatments for Mental Disorders: Current Status and Future Directions
8:30 a.m. - 11:30 a.m.

The CORE Study: Is Maintenance ECT Effective

Charles H. Kellner, M.D.
University of Medicine and Dentistry of New Jersey

While ECT is acknowledged to be the most effective short-term treatment for depression, no large-scale systematic studies have investigated the use of ECT as a continuation or maintenance treatment. The CORE Continuation ECT vs. Pharmacotherapy study was designed to assess the relative efficacy of a standardized course of continuation ECT compared with the medication combination of lithium and nortriptyline in preventing depressive relapse in a cohort of unipolar patients who remitted with an acute course of bilateral ECT. 530 patients entered, 396 patients (75%) completed the acute ECT phase, and 201 patients were randomized to the 2 treatment arms. The study was completed in May 2004. In this presentation, data from the acute phase ECT (pre-randomization) trial will be presented. 87% of patients who completed the ECT trial met strict remitter criteria. Among the total sample, treating dropouts as non-remitters, 65% met remitter criteria. Patients with psychotic depression (30.4% of the sample) remitted at an even higher rate (94% among completers, 70% among total sample). Patient ratings of suicidality decreased rapidly. These data are from one of the largest ECT cohorts in the modern literature. Efficacy and neurocognitive test data from the randomized portion of the trial will be forthcoming.

Petrides G, Fink M, Husain MM, Knapp R, Rush AJ, Mueller M, Rummans TA, O'Connor KM, Rasmussen KG, Bernstein HJ, Biggs M, Bailine SH, Kellner CH: ECT Remission Rates in Psychotic Versus Non-Psychotic Depressed Patients: A report from CORE. JECT 2001; 17: (4):244-253.

Improving the Delivery of Seizure Therapies

Sarah Lisanby, M.D.
Columbia University

ECT remains an important treatment for severely depressed patients, but its use can be limited by its cognitive side effects. Novel means of delivering the convulsive stimulus are under development to improve the risk/benefit ratio of convulsive therapy. These methods include the development of electrode configurations to apply focused electricity directly or to induce electricity indirectly using magnetic stimulation. Magnetic seizure therapy (MST) was developed as a possible means to lower the side effects of ECT through enhanced control over the site of stimulation and seizure initiation. Recent research suggests that strategies to focus current and seizure initiation in prefrontal cortex may enhance efficacy. Likewise, limiting current and seizure spread in medial temporal lobes might be expected to reduce side effects. However, the application of an electrical stimulus across the scalp results in significant shunting of current through the scalp and skull and offers little control over current spread. Since magnetic fields pass through tissue without impedance, seizure induction using magnetic fields offers the promise of more precise control over induced electrical current and seizure initiation. MST involves the induction of a seizure under general anesthesia using transcranial magnetic stimulation. This presentation will review the development of MST, from device development, to pre-clinical testing, to clinical trials. Preliminary results indicate that seizures induced with MST have a better acute side effect profile than those induced with ECT. Results of clinical trials on the antidepressant efficacy of MST will be presented.

PANEL 6 (continued)
Somatic Treatments for Mental Disorders: Current Status and Future Directions
8:30 a.m. - 11:30 a.m.

Transcranial Magnetic Stimulation in the Treatment of Mental Disorders

David Avery, M.D.
University of Washington School of Medicine

Transcranial magnetic stimulation (TMS) is a promising treatment for depression and may be useful in other mental disorders. This talk will review the studies of depression comparing TMS and electroconvulsive therapy, and TMS and sham conditions including a recent sham-controlled study of TMS in patients with Major Depression who have failed at least two antidepressant trials. In addition, future directions for TMS research will be considered including 1. using a greater number of pulses, higher intensity and more sessions and 2. application of TMS in other psychiatric disorders.

Educational Objectives:
1. Understand the basic principles of TMS and the TMS treatment parameters.
2. Understand the database of the TMS studies and the methodological issues concerning these studies.
3. Appreciate the potential of TMS in treating other psychiatric disorders.

Vagus Nerve Stimulation

A. John Rush, M.D.
University of Texas Southwestern Medical Center

This presentation will review the rationale for vagus nerve stimulation (VNS) therapy in depression, as well as available acute phase, and longer-term clinical studies of VNS as an adjunctive treatment. Comments will be provided on where, if found to be effective, VNS might fit in a step-wise treatment program for treatment resistant depression.

Educational Objectives:
1. Understand the rationale for considering VNS in the treatment of depression.
2. Understand the available efficacy and safety data on VNS obtained in brief and longer-term trials.

PANEL 6 (continued)
Somatic Treatments for Mental Disorders: Current Status and Future Directions
8:30 a.m. - 11:30 a.m.

Deep Brain Stimulation in Intractable OCD, and Preliminary Results in Intractable Depression

Benjamin D. Greenberg, M.D., Ph.D.
Butler Hospital, Brown Medical School
Lawrence H. Price, Gerhard Friehs, Donald Malone, Ali R. Rezai, N. Andrew Shapira, Kelly D. Foote, M.A. Okun, Scott L. Rauch, Darin Dougherty, Georg Noren, Paul F. Malloy, Steven Salloway, Richard Marsland, Audrey Tyrka, Linda Carpenter, Wayne Goodman, Steven A. Rasmussen

Deep Brain Stimulation (DBS) is an FDA-approved treatment for movement disorders. We are studying the safety and efficacy of DBS of the anterior limb of the internal capsule in patients with obsessive-compulsive disorder (OCD) of disabling severity, refractory to sustained efforts with all proven conventional medication and behavior therapies. Ten patients with intractable OCD have been enrolled in a collaborative trial at Butler Hospital/Brown University, the Cleveland Clinic, and the University of Florida. After multidisciplinary assessment and independent review of diagnosis, adequacy of prior treatment, and informed consent capacity, these 10 patients had custom-made DBS brain leads implanted bilaterally in the anterior limb of the internal capsule and adjacent ventral striatum. This stimulation target was developed using our group's prior experience with gamma knife anterior capsulotomy for OCD and the initial experience with DBS of B. Nuttin and colleagues in Leuven, Belgium. After a 3-week post-implantation rest, patients began a period of stimulation optimization and active DBS. Patients and symptom raters were unaware of stimulation condition. At on average 6 months later, 4 of the 10 patients met our stringent response criteria of at least a 35% reduction in scores on Yale-Brown Obsessive-Compulsive Scale plus at least a 15 point gain on the Global Assessment of Functioning scale. No patients experienced persistent adverse effects. These results compare favourably with those 6 months after gamma capsulotomy. Additional safety and efficacy data in intractable OCD will be presented, together with preliminary results using DBS at the same target in intractable depression.

Objectives:
1. To describe brain imaging studies that attempt to isolate the neural pathways associated with response to existing treatments in OCD and depression.
2. To relay new information on the development and results of deep brain stimulation in research and treatment of refractory OCD.
3. To describe the pilot experience with deep brain stimulation in intractable depression.

TREATMENT DEVELOPMENT SESSION 5
Impulsivity and Aggression as Clinical Treatment Targets
9:00 a.m. - 12:00 p.m.

Overview

Impulsivity and aggression are common psychiatric symptoms, either with or without concomitant DSM-IV diagnoses. This panel will explore aspects of impulsivity and aggressiveness, including possible treatment approaches.

Dr. Coccaro will present an overview of impulsivity and aggression, discussing the relationship between these symptoms and psychiatric diagnosis.

Dr. Blair will discuss studies suggesting that anterior cingulate, orbital frontal cortex, the nucleus accumbens and the amygdalae play specific roles in the pathophysiololgy of the impulse control disorders. As different pathologies impact on different systems, the behavioral sequelae diverge across conditions. In addition, the selective impact of differential neurotransmitters on these systems will be considered together with the implications of these findings for the management of impulse control disorders.

Dr. Wozniak will discuss ways to recognize impulsivity as a common characteristic of pediatric bipolar disorder and ADHD. She will also discuss symptoms that differentiate the two disorders.

Dr. DelBello will discuss methods to assess treatments for impulsivity associated with Bipolar Disorder and comorbid disorders.

Dr. Mattes will discuss revised criteria for Intermittant Explosive Disorder and will present recent final data from a double-blind placebo-controlled oxcarbazepine trial (N = 48), discussing factors which may account for the more consistent evidence of efficacy than that found in prior studies.

Dr. Potter will present a drug company's perspective on developing treatments for impulsive aggression.

Drs. Hollander and Laughren will discuss the above. Dr. Hollander will focus on the phenomenology of impulsivity and aggression. Dr. Laughren will discuss the FDA's perspective on approving a drug for symptomatic treatment (e.g. for impulsive aggression) or for a non-DSM-IV diagnosis.

Learning Objectives:
1. Explain the neurobiology and pathogenic mechanisms responsible for impulse control problems.
2. Recognize impulsivity and aggression as common characteristics of a spectrum of comorbid disorders and discuss methods of treating affected children, adolescents and adults.
3. Discuss diagnostic and methodological features important in studying medication effects in patients with impulsive aggression.

TREATMENT DEVELOPMENT SESSION 5 (continued)
Impulsivity and Aggression as Clinical Treatment Targets
9:00 a.m. - 12:00 p.m.

Diagnostic and Methodologic Advances in Evaluating Medications for Adult Intermittent Explosive Disorder

Jeffrey A. Mattes, M.D.
Psychopharmacology Research of Princeton

Stimulated by a placebo-controlled study which demonstrated consistent evidence of benefit from oxcarbazepine in adults with impulsive aggression, this presentation will focus on diagnostic and methodologic features which may explain these results, given the less consistent results found in prior studies.

The DSM-IV criteria for Intermittent Explosive Disorder seem to be overly restrictive. Modified criteria, proposed by Coccaro et al, include patients with less severe aggressiveness (e.g., just verbal aggressiveness) and do not exclude patients who have other diagnoses associated with aggressiveness (e.g., Borderline Personality, PTSD, ADHD), if aggressiveness is the primary clinical concern. These modified criteria allow for feasible recruitment.

The modified Overt Aggression Scale (yielding a calculated score based on the frequency and severity of different types of aggressiveness) is the most widely used primary efficacy measure in studies of impulsive aggression, but its face validity is poor; frequent mild aggression can score higher than less frequent more severe aggression. A global rating of overt aggression (originally from the SADS-C) seems preferable (data will be reviewed).

Since baseline scores of aggressiveness may be less stable than for other psychiatric symptoms (e.g., depression), covariance analyses may be preferable to analyses of Change Scores. Also, attempts to increase patient retention (e.g., offering free post-study treatment) are important in this population (early dropouts reduce power). Finally, trials must be long enough (6-10 weeks) for the expected initial placebo response to dissipate. All of these issues will be reviewed.

With the specified diagnostic entry criteria, outcome measures, and other design features, it may be possible to consistently demonstrate medication efficacy for impulsive aggression.

Educational Objectives:

1. Learn about modifications to DSM-IV criteria for Intermittent Explosive Disorder which make sufficient study recruitment feasible.
2. Learn about ratings and other design features which increase the likelihood of demonstrating medication benefit in studies of patients with impulsive aggression.

PANEL 7
Treatment of Mood Disorders Associated with the Reproductive Cycle: Benefits and Risks
10:00 a.m. - 12:00 p.m.

Valproate Predisposes to Polycystic Ovarian Syndrome in Women with Bipolar Disorder

Hadine Joffe, M.D., M.Sc., Lee S. Cohen, M.D., Wren L. McLaughlin, Judith M. Adams, D.M.U., Francine J. Molay, M.S.W., Cindy H. Hwang, Janet E. Hall, M.D.*, Gary S. Sachs, M.D. *
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* contributed equally as senior author

Background: Evidence suggests that valproate may predispose to polycystic ovarian syndrome (PCOS) in women with epilepsy, but epilepsy may explain this apparent association. The development of PCOS after valproate use was therefore examined in women taking valproate for bipolar disorder.

Method: 300 women with bipolar disorder (age 33.1 ± 7.3 years) were evaluated for evidence of PCOS and PCOM at 16 Systematic Treatment Enhancement Program for Bipolar Disorder sites. PCOS was defined by infrequent menses (<10 in past year) and evidence of hyperandrogenism (at least one of hirsutism, moderate-to-severe acne, male-pattern alopecia, and elevated serum levels of total testosterone, calculated free testosterone, and dehydroepiandrosterone-sulfate). After excluding women with PCOS predating use of mood-stabilizers (n=14), use of birth-control pills (n=54) and progestin therapy (n=2), and PCOS features occurring together with oligomenorrhea that was explained by an elevated serum prolactin (n=1), thyroid-stimulating hormone (n=0), or follicle-stimulating hormone (n=0), 229 women were evaluable for treatment-emergent PCOS. Pelvic ultrasounds were performed and interpretable in 184 (80.3%) of the women who were evaluated for treatment-emergent PCOS.

Results: Subjects evaluable for current PCOS included 86 valproate-users and 143 non-users (65 lithium, 52 lamotrigine, 29 topiramate, 26 gabapentin, 15 carbamazepine, 11 oxcarbazepine). Nine (10.5%) valproate-users versus 2 (1.4%) non-users (1 lamotrigine, 1 gabapentin) had treatment-emergent PCOS (relative risk 7.5, 95% CI 1.7-33.8, p=0.002). Among valproate users with treatment-emergent PCOS, infrequent menses developed after a median of 3 months (range 1-12 months) of valproate use. Compared with valproate users without PCOS, valproate users with treatment-emergent PCOS had a higher body-mass index (median 36.0, range 25.8-47.5 vs. 26.3, range 17.7-52.9 kg/m2, p=0.01) and insulin resistance (median HOMA-IR 3.1, range 0.6 8.1 vs. 1.7, range 0.4 12.2, p=0.02). PCO morphology occurred as commonly in valproate users as non-users (20/67, 29.9% vs. 29/117, 24.8%, p=0.46).

Conclusions: Valproate induces PCOS, with rapid onset of menstrual-cycle abnormalities, and is associated with obesity and insulin resistance. Valproate use is not associated with an increased prevalence of PCO morphology. Attention to reproductive-system characteristics is important in managing women with bipolar disorder who are treated with valproate.

Source of Funding: This study was sponsored by NIMH contracts (Massachusetts General Hospital, University of Pittsburgh, and University of Texas, San Antonio) and Abbott Laboratories, Inc.

Thursday, June 3, 2004 (continued)

PANEL 7 (continued)
Treatment of Mood Disorders Associated with the Reproductive Cycle: Benefits and Risks
10:00 a.m. - 12:00 p.m.

FDA Pregnancy Labeling Changes

Kathleen Uhl, M.D.
Food and Drug Administration

The FDA Pregnancy Labeling Task Force is working to improve the quantity and quality of data available in product labeling on the use of drugs during pregnancy and is in the process of revising the regulations that govern pregnancy labeling to delete the pregnancy category scheme and promote the inclusion of more useful clinical information in a narrative format. The pregnancy section of product labeling usually contains data from animal reproductive toxicity studies. Even after years of marketing, labels are rarely updated to include human experience with the product. Inclusion of appropriate human pregnancy exposure data in product labeling requires analysis of data sources and interpretation of the results to provide clinically meaningful data in labeling. Human data sources include isolated case reports, case series, published literature, and pregnancy exposure registries. Examples of labeling that have incorporated human pregnancy exposure data will be presented. The inclusion of clinically relevant human pregnancy data in product labeling will assist health care providers and their patients in making decisions regarding the use of drugs in pregnancy and will provide useful information for treating or counseling patients who are pregnant or anticipating pregnancy.

Educational Objectives:

- Understand important upcoming changes to the pregnancy section of labeling.
- Demonstrate real-life examples of the pregnancy section of labeling that have incorporated human pregnancy data.
- Appreciate the utility of more clinically relevant information in the pregnancy section of labeling.

PANEL 8
Developing Networks for Clinical Research
10:30 a.m. - 12:00 p.m.

Lessons Learned from Primary Prevention Trials sponsored by the National Cancer Institute (NCI)

Lori M. Minasian, M.D.
National Cancer Institute

The successfully executed primary prevention trials sponsored by NCI represent an expansion of an established research agenda within the well-developed clinical trials infrastructure of the NCI Cooperative Groups. Since 1983, a community-based network (the Community Clinical Oncology Program) has been connected with the Groups and forms the primary infrastructure for the cancer prevention trials. Building the network is 90% of the battle for the NCI prevention trials.

At the core of building an effective network is educating physicians, nurses, and the public about the differences between cancer treatment and prevention clinical trials. For the oncology community, clinical trials are the Gold Standard for treatment. Patients are frequently recruited onto treatment trials as part of routine practice, and view their participation as part of their treatment.

PANEL 8 (continued)
Developing Networks for Clinical Research
10:30 a.m. - 12:00 p.m.

Lessons Learned from Primary Prevention Trials sponsored by the National Cancer Institute (NCI) (continued)

However, the patient motivation for participation in prevention trials is different. These differences must be considered in planning recruitment strategies.(6) As "at risk" individuals do not routinely walk into oncologist's offices, oncology practices have to develop an outreach program and/or actively establish relationships with other specialists who may see patients with pre-malignant conditions or with primary care physicians and practices for the referral of at risk individuals or healthy participants that may wish to participate in cancer prevention clinical trials.

Successful recruitment strategies require educational efforts at many levels that target both the public and professionals. A communication plan for disseminating recruitment and retention materials is critical. Though it may be a national study, the recruitment is local. Regular workshops for training of research staff, email updates, newsletters for participants are part of the communication links that help everyone keep engaged in the trial. Local study site interactions with participants are also crucial to success. The communications efforts should be developed that fit the study design. For example, a large mass media campaign can be successfully implemented in trials with broad eligibility and agents with low toxicity such as SELECT (A). Additionally, minority recruitment should be planned for well in advance (B, C).

The trial design can impact both recruitment and retention. The more complicated the trial design, the more difficult the study is to explain to investigators and potential participants. Also, cancer prevention trials are lengthy, frequently lasting more then 5 years. Lengthy trials quickly become complicated and require continuous adaptation to changes in the standard of care.

The NCI cancer prevention trials were all conducted in a clinical research network with extensive experience in the conduct of cancer clinical trials. The coordinating centers for the prevention trials could draw upon their skill, experience, and infrastructure developed through the treatment trials for efficiencies. This includes standardized procedures and definitions, centralized support services and procedures. However, the data management and collection for large primary prevention trials are not identical to treatment trials, with the volume of data collection being a major difference.

How can this information be useful to NINDS? NCI has had the luxury of building upon an existing network. This poses a particular challenge regarding initiating large trials of primary stroke prevention, as no infrastructure exists. Collaboration with primary care physicians is likely to be necessary.

For a primary stroke prevention trial some design issues to keep in mind would be keep the trial simple and short.

Additional publications:

1. Minasian L, Smigel Croker K, Ryan A, Voss A, Cave L, Kelin E, Ford L. Effectiveness of a Media-Based Launch to Recruit to a Prostate Cancer Prevention Trial. Controlled Clinical Trials 24(3S): 50S, June 2003.
2. Moinpour CM, Atkinson JO, Thomas SM, Underwood SM, Harvey C, Parzuchowski J, Lovato LC, Ryan AM, Hill MS, Deantoni E, Gritz ER, Thompson IM Jr, Coltman CA Jr. Minority recruitment in the prostate cancer prevention trial. Ann Epidemiol. 2000 Nov;10(8 Suppl):S85-91.
3. Thompson IM Jr, Kouril M, Klein EA, Coltman CA, Ryan A, Goodman P. The Prostate Cancer Prevention Trial: Current status and lessons learned. Urology. 2001 Apr;57(4 Suppl 1):230-4.

UPDATE SESSION II
1:00 p.m. - 2:15 p.m.

Insulin Coma Therapy Revisited

Jonathan O. Cole, M.D.
McLean Hospital
Tara Sorrentino

Insulin coma therapy was discovered by Manfred Sakel while using newly available insulin at a drug detox hospital. Treatment widely used in Europe and the United States for 20 years. Many clinicians reported major remission/improvement rates in the 70-80% range in schizophrenics ill less than 12 months. Remissions (as in the case of John Nash) often lasted over a year after last of 30-60 coma sessions. Arrival of convulsive therapies displaced insulin (cheaper maybe safer) somewhat. Arrival of phenothiazines (much cheaper, easier to use) in the 1950's led insulin coma to gradually be abandoned in the United States. Controlled/comparative studies, mainly small or flawed, failed to show insulin superior to chlorpromazine.

It now appears that in Russia insulin coma has been used along side of the antipsychotic drugs for 50 years and is valued by ex-Russian Israeli psychiatrists. We are attempting a meta-analysis of Western and Russian reports on efficacy of insulin coma.

We hope to answer senior author's questions:

- Does Insulin Coma give better or longer remissions than neuroleptics?
- Does it work in different groups of patients?
- Does occurrence of seizures during insulin coma affect response?

The senior author's positive experience in running an insulin coma unit in the United States Army in 1953 has led him to initiate this review.

Seasonal Affective Disorder (SAD): Two Decades of Progress

Norman E. Rosenthal, M.D.
Georgetown Medical School

Seasonal Affective Disorder (SAD), first described twenty years ago, is a condition of recurrent depressions occurring in autumn and winter, alternating with non-depressed periods in spring and summer. During winter depressions patients often report decreased energy, overeating, oversleeping and carbohydrate craving along with depression and anxiety. The prevalence of SAD increases with latitude and may be as high as 9% in northern parts of the U.S. SAD appears to result from three factors: biological vulnerability, stress and decreased environmental light, which, to be effective, must be bright enough (e.g. 10,000 lux), given for long enough (e.g. 30 to 90 minutes/day) and properly timed (generally in the morning). Devices designed to simulate a summer dawn may also be therapeutic. Although light therapy is helpful in many cases, some patients fail to respond adequately, while others find treatments unacceptably time-consuming or inconvenient. Side-effects of light therapy include headaches, eyestrain and irritability. There have been several antidepressant trials to treat seasonal depressive episodes, but most have involved sample sizes. Notably, however, in a recent large multicenter study, researchers prevented the onset of seasonal depression in some patients by initiating treatment with Wellbutrin-XL in the fall or winter prior to the onset of depression. Further studies of antidepressants in SAD are needed for those afflicted by dark winter days, who are seeking improved treatment options.

TREATMENT DEVELOPMENT SESSION 6
Models and Objective Measures Relevant to Impulsivity in Mental Disorders
2:15 p.m. - 4:15 p.m.

Overview

The overall goal of this session is to explore which aspects of clinical impulsivity are most amenable to developing objective parallel measures in humans and animals. Discussion will also address possible areas of neurobiological research on impulsivity that may be ready for translation to clinical studies. John Evenden will lead the session with a discussion of the use of animal models of impulsivity in pharmacological studies aimed at the discovery and development of new treatments. Brian Knutson will then describe behavioral and physiological measures and models of reward in humans. Harriet de Wit will conclude the session with a presentation of data from studies investigating impulsive behavior using parallel procedures in humans and rats. Talks will be followed by discussion led by William Potter and Lois Winsky.

New Frontiers in the Conceptualization and Visualization of Impulsivity

Brian Knutson, Ph.D.
Stanford University

Empirical progress in the neuroimaging of impulsivity requires clear definitions and operationalizations. This talk will explore the possibility of defining impulsivity componentially as a function of the combined activity of motivational and reflective systems, and will review recent FMRI evidence that dynamic activity of at least one motivational system can be isolated and visualized. These findings have implications for imaging pharmacotherapeutic modulation of brain activity in children.

Educational Objectives:
1. Understand a componential definition of impulsivity.
2. Learn about recent findings in FMRI studies of appetitive motivation.
3. Consider pharmacotherapeutic implications of FMRI studies of impulsivity.

Assessment of Impulsive Behavior in Humans and Non-Humans

Harriet de Wit, Ph.D.
University of Chicago

Impulsive behavior is a central feature of many psychiatric disorders, including substance abuse. However, there has been little consensus about the basic underlying behavioral or neural processes that mediate impulsivity. Recent evidence suggests that there are at least two subtypes of impulsive behavior, one related to cognitive decision-making and the other related to behavioral inhibition. Data will be presented from studies investigating these forms of impulsive behavior using parallel procedures in humans and rats. These studies, which use delay discounting to measure cognitive decision-making and a Stop Task to measure behavioral inhibition, illustrate the potential power of conducting parallel cross-species studies, and extend our understanding of the basic behavioral and neural mechanisms underlying impulsivity.

Educational Objectives:
1. To understand the multidimensional nature of impulsive behavior.
2. To learn about procedures that can be used with both human and non-human subjects to assess two specific subtypes of impulsive behavior.
3. To appreciate the power of conducting parallel studies of behavioral processes using both humans and non-humans.

PANEL 9
Advances in the Treatment of ADHD from Preschool to Adulthood
4:00 p.m. - 6:00 p.m.

Diagnosing ADHD in Preschool Children

Jaswinder K. Ghuman, M.D.
University of Arizona

Objective: Attention deficit/hyperactivity disorder (ADHD) often begins in preschool years and has been shown to be stable over time. Frequently, there is accompanying impairment including emotional distress in the preschool child and the caregivers, expulsion from daycare or early education settings and excessive demands on the caregiver's time. Diagnosing ADHD in preschool children is a challenging task due to rapid developmental change, high levels of developmentally appropriate activity and importance of contextual variables during the preschool years. Nevertheless, early diagnosis and early intervention is important, since delay in diagnosis and treatment may result in developmental deviance and further promote perturbed development, kindle further psychopathology, and may lead to disturbance in family functioning.

Methods: In this presentation, we will discuss the current state of knowledge regarding approaches to diagnosing ADHD in preschool children and assessment process utilized in clinical practice and research.

Results: In the DSM-IV field trials, 75% of the children meeting the DSM-IV diagnostic criteria for the Predominantly Hyperactive/Impulsive subtype were less than 6 years of age. Diagnosis of ADHD was associated with functional impairment even after controlling for comorbid psychiatric disorders. In a recent epidemiological study, the overall prevalence of ADHD was found to be 5.1%; mean age of onset was 2 & ½ years; and preschoolers with ADHD were significantly impaired.

Diagnostic process used in the NIMH Preschool ADHD Treatment Study (PATS) included measures from multiple informants, methods, settings and perspectives to aid in the ADHD diagnosis of the preschool study participants. Additionally, clinical narrative for each child was discussed in a weekly conference call and required unanimous affirmative vote regarding the ADHD diagnosis.

Conclusion: There is continued controversy regarding ADHD diagnosis in preschool children. Specificity of ADHD diagnosis in preschool children can be enhanced if supported by a history of multiple impairments that occur in multiple contexts and in multiple situations/ environments and by obtaining information from multiple raters. Additionally, functional impairment should be assessed in the areas of interference with the child's developmental progress, learning, relationships with authority figures, peer relationships, self-image and stress on the environment.

PANEL 9 (continued)
Advances in the Treatment of ADHD from Preschool to Adulthood
4:00 p.m. - 6:00 p.m.

Rationale and Design of the Preschoolers with ADHD Treatment Study (Pats).

Scott H. Kollins, Ph.D.
Duke University Medical Center

Objective: The diagnostic validity of Attention Deficit Hyperactivity Disorder (ADHD) has been supported in preschool children (3-5 years). Compared to school-aged children with ADHD, however, little pharmacological treatment research has been conducted with preschool children, in spite of the fact that rates of off-label prescriptions have risen recently. The objective of the PATS was to evaluate safety and efficacy of methylphenidate in preschoolers with ADHD.

Methods: Seven primary phases comprised the PATS study: Screening/Assessment; Parent Training; 1-week open label safety titration; 5-week double-blind placebo controlled titration trial evaluating placebo, 1.25 mg, 2.5 mg, 5.0 mg, and 7.5 mg weekly; 4-week double-blind placebo controlled parallel group study evaluating placebo and best dose determined in the previous phase; 10-month open label maintenance; and a 6-week double blind placebo discontinuation trial. The primary efficacy outcome measure is a composite score from parent and teacher rating scales of ADHD symptom severity from the 5-week crossover phase. Vital signs, including height and weight, and treatment-emergent adverse events and served as the primary safety evaluations.

Results: Of the 303 patients who passed screening, 183 entered the open label safety phase; 165 were randomized into the crossover portion of the trial and comprised the intent-to-treat sample. Eight-nine percent (N=147) of patients randomized completed the crossover phase and 114 were enrolled in the parallel group phase. One hundred forty patients were enrolled in the maintenance phase.

The Rupp Methylphenidate Study in Children with Pervasive Developmental Disorders

Larry Scahill, M.S.N., Ph.D.
Yale Child Study Center
Benedetto Vitiello, MD, Michael Aman, PhD, James McCracken, MD, Christopher McDougle, MD, Elaine Tierney, MD, Mark Davies, MPH, Eugene Arnold, RUPP Autism Network

Objective: To report on a placebo-controlled, crossover study of methylphenidate (MPH) in children with pervasive developmental disorders and hyperactivity.

Methods: Subjects entered a one-week test dose phase to determine drug tolerability before receiving placebo and three different doses (low, medium, high) of MPH in a four-week randomized crossover trial.

Results: 117 subjects were screened; 72 were enrolled. Six subjects (8.3%) had intolerable side-effects to MPH during the test dose period; 66 subjects entered the randomized crossover phase. Of these, 7 subjects exited due to adverse effects (e.g., irritability, insomnia, loss of appetite); 1 subject withdrew consent. Based on parent and teacher ratings as well as the Improvement score on the Clinical Global Impression rated by a blinded clinician, the MPH positive response rate was 49% (35/72); 9 (12.5%) subjects showed a positive response to placebo. Each dose level of MPH was associated with significant reductions on the Aberrant Behavior Checklist Hyperactivity subscale as rated by parents and teachers; effect sizes was 0.3 for the lowest dose (0.18 mg/kg/dose) to 0.5 for the highest dose (0.5 mg/kg/dose), suggesting a modest dose effect.

Conclusion: MPH was superior to placebo in approximately 50% of enrolled subjects. Both the response rate and magnitude of effect were lower than what is observed in typically developing children with attention-deficit/hyperactivity disorder. Adverse effects were similar, but appear to be more frequent in children with PDD.

PANEL 9 (continued)
Advances in the Treatment of ADHD from Preschool to Adulthood
4:00 p.m. - 6:00 p.m.

Diagnostic Controversies in Adult ADHD

James J. McGough, M.D.
Neuropsychiatric Institute and David Geffen School of Medicine at UCLA

Objective: While adult Attention Deficit Hyperactivity Disorder (ADHD) is of increasing clinical and research interest, there is no consensus on valid approaches to diagnosis. Without clearly validated adult criteria both clinicians and researchers risk misdiagnosis and prescription of unnecessary or inadequate treatments. This presentation will contrast competing assessment strategies, highlight difficulties with current diagnostic criteria, and recommend optimal approaches for evaluation of adult ADHD.

Method: Diagnostic approaches including the Wender Utah Criteria, DSM criteria, and laboratory assessment strategies will be discussed. Advantages and disadvantages of each approach will be described as a basis for current clinical practice and research design.

Results: Both Wender Utah criteria and DSM-based methods identify significantly impaired ADHD adults with neurocognitive and biological patterns similar to pediatric ADHD patients. Wender Utah criteria established the need for retrospective childhood diagnosis and recognize developmental differences in adult symptoms. Wender Utah criteria ignore the predominately inattentive subtype and exclude some patients in the presence of significant comorbid psychopathology. Wender Utah criteria diverge significantly from the DSM conception of ADHD. DSM criteria are not developmentally appropriate for adults and symptom diagnostic thresholds have never been validated in adult patients. Current DSM criteria are not sensitive for diagnosis in some adults with significant ADHD related impairment, and exclude some patients that would benefit from treatment. There are insufficient scientific data to justify use of neuropsychological tests, brain imaging studies, or other laboratory assessments in clinical diagnosis of adult ADHD.

Conclusion: Adult ADHD remains a clinical diagnosis. Current recommendations for diagnosis of adult ADHD include use of semi-structured instruments to probe childhood and current symptoms, collaboration of clinical information with third party sources, broad interpretation of age-of-onset criteria, evaluation of impairment in multiple domains, and careful assessment of comorbid psychopathology. Scientific validation of diagnostic criteria for adult ADHD would benefit both clinical practice and research.

PANEL 9 (continued)
Advances in the Treatment of ADHD from Preschool to Adulthood
4:00 p.m. - 6:00 p.m.

Medication and Psychosocial Treatment of Adults with Attention Deficit Hyperactivity Disorder (ADHD).

Lily Hechtman, M.D.
McGill University Health Center

Background: The systematic diagnosis and treatment of adults with ADHD is relatively new, and there are few studies that have addressed this issue in a controlled, rigorous fashion. The treatment of adults with ADHD is complicated by the fact that symptoms are ego-syntonic and comorbid anxiety, depression, and substance abuse are frequent. The aim of this presentation is to review other studies and to present data from our studies that have explored the medication and psychosocial (cognitive behavioral therapy, CBT) treatment of adults with ADHD.

Methods: We will compare the strengths and weakness of studies in the literature that explored the efficacy and side effects of stimulant medication in adults with ADHD (e.g., Wood et al., 1970, Wender et al., 1980, 1986, Spencer et al., 1995, 1999, Bouffard et al., 2003). Studies of non-stimulant medications, such as atomoxetine, bupropion, venlafaxine, tricyclics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors will also be reviewed. In addition, we will present data from our multisite study, which compared the relative efficacy of Dexedrine, Paroxetine, both medications, and placebo in a randomized, four-parallel group design of adults with ADHD who had some comorbid anxiety and depression. Studies involving psychosocial treatments of adults with ADHD, such as psychoeducational approaches, psychotherapy, behavior and CBT will be reviewed. We will present our pilot data on a 13-week group CBT program for adults with ADHD.

Results: Studies suggest that stimulants at dosages ranging from .6 to .9mg/kg/day are effective for adults with ADHD. Side effects are similar to those seen in children though cardiovascular side effects may be clinically more important in adults. Non-stimulant medications, such as atomoxetine, bupropion, venlafaxine, tricyclic antidepressants are also helpful though less effective than stimulants for ADHD symptoms. However, many adults with ADHD are comorbid for anxiety and depression, and some of these medications may address both problems. Psychosocial approaches, particularly CBT, hold some promise.

Conclusions: Short-term studies have shown stimulants and CBT to be effective in treating adults with ADHD. However, treatment (both medication and psychosocial) of adults with ADHD is a relatively new and promising area of research. The efficacy of various drugs (stimulants and non-stimulants) and drug combinations over longer periods need to be rigorously tested, particularly for adults with ADHD who are comorbid for other conditions. Psychosocial treatment, particularly CBT, with and without medication also needs more long-term studies.

Thursday, June 3, 2004 (continued)

PANEL 9 (continued)
Advances in the Treatment of ADHD from Preschool to Adulthood
4:00 p.m. - 6:00 p.m.

An Overview of the Drug Development Process for a Product with a Primary Pediatric Indication

Albert J. Allen, M.D., Ph.D.
Lilly Research Laboratories

This presentation will review the drug development process in the United States, focusing on practical issues and new FDA regulations and guidance for developing a drug with a primarily pediatric indication. Atomoxetine, a novel treatment for attention-deficit/hyperactivity disorder (ADHD) recently approved in the United States, will be used to illustrate how the modern drug development process works. It will also highlight changes in the development of ADHD treatments since the introduction of stimulants over 50 years ago. In addition to dealing with unique regulatory requirements and guidance, developing a drug for use in a pediatric population poses special challenges in diverse areas including biomedical ethics, developmental pharmacology, and clinical trial design and implementation.

Learning Objectives:

- Familiarize participants with drug development process for a compound with a primarily pediatric indication and new regulations.
- Review challenges associated with developing pediatric treatments.

Friday, June 4, 2004

FDA SYMPOSIUM
9:00 a.m. - 12:00 p.m.

Comparative Claims for Psychiatric Drug Products

Thomas Laughren, M.D.
Food and Drug Administration

Information on the comparative risks and benefits among drugs in a class is potentially valuable information for prescribers, if the information is valid. This talk will explore the regulatory issues that need to be addressed in considering comparative claims. Study designs for superiority and noninferiority claims will be discussed. The important challenge in a comparative study is to ensure "fairness" of the comparision, and several principles will be provided for meeting this challenge, including: (1) equi-effective doses; (2) optimal use of comparator; (3) selecting an appropriate comparator; (4) using sensitive assessment measures; (5) selecting an unbiased population; (6) comparing in all important domains; (6) comparing at all relevant times; (7) replication.

Educational Objectives:

- Understand the types of comparative claims that might be sought.
- Understand design issues and hypothesis testing for studies to support superiority and noninferiority claims.
- Appreciate the principles for ensuring fair comparisons with regard to comparative safety and efficacy claims.

FDA SYMPOSIUM (continued)
9:00 a.m. - 12:00 p.m.

Patient-Reported Measures as Clinical Trial Endpoints: What Are the Issues?

Laurie B. Burke, R.Ph., M.P.H.
Food and Drug Administration

Medical product manufacturers often seek to measure outcomes from the perspective of the patient for use in product labels and advertising. Patient reports of their disease and treatment experience present unique measurement development and validation issues that impact the study design, data analysis, and data interpretation. Adequacy of a patient-reported measure is specific to the study objectives, the study population, the disease or condition treated, and the statistical analysis plan. This talk will explore these issues from a regulatory perspective.

Educational Objectives:

1. Understand the broad range of regulatory issues that exist when developing a medical product claim based on a patient-reported outcome measure.
2. Understand and appreciate the development and validation process involved when a patient-reported outcome is planned for a phase 3 clinical trial.

SSRI/SNRI Syndromes: Discontinuation Symptoms in Adults and Discontinuation or Toxicity Symptoms in Neonates

Robert Levin, M.D.
Food and Drug Administration

Treatment discontinuation of SSRI/SNRI drugs, especially when abrupt, has been associated relatively commonly with each drug of these classes. Characteristic withdrawal/discontinuation symptoms from among six clusters will be discussed. While symptoms are usually mildly to moderately severe, some patients may temporarily develop significant dysfunction. The clinician needs to be aware of such potential adverse events. Thus, the Division has proposed new class labeling for SSRI/SNRI drugs.

Neonatal complications, with nearly all of these drugs, have been associated with in utero SSRI/SNRI exposure as well. In some respects, the neonatal symptoms resemble the discontinuation symptoms observed in adults; however, in some cases, neonatal symptoms may be consistent with SSRI/SNRI toxicity syndromes. As in adults, neonatal symptoms range from mild to severe. For reasons described above, the Division has proposed class labeling for SSRI/SNRI drugs.

Educational Objectives:

- Discuss various aspects of the SSRI/SNRI discontinuation syndromes seen in adults.
- Describe the nature of SSRI/SNRI syndromes observed in neonates exposed to SSRI/SNRI drugs in utero.
- Present the proposed class labeling language regarding these adverse events.
- Provide the rationale for proposing the class labeling.

POSTER ABSTRACTS TOPIC INDEX

ODD-NUMBERED POSTERS PRESENTED ON WEDNESDAY
EVEN-NUMBERED POSTERS PRESENTED ON THURSDAY

All poster presentations are copied verbatim and appear in category listing per day as outlined below:

Poster Session I (Wednesday, June 2, 12:15 p.m. - 2:15 p.m.):

Primary Topic	Poster Number
ADHD	3, 5, 7, 9, 11, 13
Alcohol/Substance Use Disorder	1, 15
Anxiety Disorder (other than OCD)	17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49
Bipolar Disorder	51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 219, 279, 285, 289, 299, 301
Childhood/Adolescent Disorder (other than ADHD)	105,107, 109, 111, 113, 115, 117, 119, 121
Comorbid Mental and Physical Disorders	123
Comorbid Mental and Substance Use Disorders	125, 127, 129, 131,133
Comorbid Mental Disorders	135
Dementia or Other Geriatric Disorder*	137, 139, 141, 143, 145, 147, 149, 151, 223, 225, 227
Depression	153,155,157,159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 291, 295, 297
Eating Disorder	221
OCD or Related Disorder	229, 231, 287
Sleep Disorder	265, 267, 269
Women's Mental Health Issues	271, 273
Other	275, 277, 281, 283, 293
Schizophrenia	233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263

Poster Session II (Thursday, June 3, 12:15 p.m. - 2:15 p.m.)

Primary Topic	Poster Number
ADHD	2, 4, 6, 8, 10, 12, 14, 16, 18, 20
Alcohol/Substance Use Disorder	22
Anxiety Disorder (other than OCD)	26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48
Bipolar Disorder	24, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 150, 152, 264, 266, 268, 282, 286, 288
Childhood/Adolescent Disorder (other than ADHD)	94, 96, 98, 100, 102, 104 , 290
Comorbid Mental and Physical Disorders	108, 110, 112, 114
Comorbid Mental and Substance Use Disorders	116, 118, 120
Dementia or Other Geriatric Disorder*	122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 208
Depression	142, 144, 146, 148, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 262, 272, 274, 278, 284
OCD or Related Disorder	210
Psychotic Disorder (other than Schizophrenia)	212, 214, 292
Sleep Disorder	106,252, 254
Women's Mental Health Issues	256, 276
Other	258, 260
Schizophrenia	216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 270, 280

POSTER NO. 1

A COMMUNITY LINKAGE INTERVENTION TO TRANSITION INDIVIDUALS WITH A CO-OCCURING SUBSTANCE ABUSE AND PSYCHIATRIC DISORDER FROM ACUTE PSYCHIATRY TO OUTPATIENT CARE

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Background: Individuals with co-occurring mental illness and substance abuse problems are often non-compliant with treatment and difficult to engage in outpatient services following discharge from Acute Psychiatry. This transitional period frequently results in a cycle of re-hospitalizations that are difficult for the individual and costly to the institution.

Objective: In an effort to improve medication compliance and outpatient treatment engagement, we developed a six-week community linkage intervention to transition individuals from Acute Psychiatry to outpatient services. This treatment blends brief and intensive case management, integrated substance abuse, and mental health therapy with a primary focus on motivational enhancement techniques.

Method: Fifty-nine dually diagnosed veterans participated in the research. Twenty-six subjects received the new Transitional Case Management (TLC) along with outpatient Mentally Ill Chemical Abuse Treatment (MICA), and 33 were discharged as usual to an outpatient MICA program.

Results: Although there were no significant differences in baseline severity between the intervention and comparison groups, the individuals in the TLC group had significantly more hospitalization days the year prior to the intervention (61 vs. 49). The veterans who received the TLC treatment had significantly better attendance at the initial outpatient screening (.02) and follow-up appointments (.001), better overall attendance in the Day Treatment Center (.001), and greater pharmacy prescription pick-ups (.11) They were also less likely to be lost to follow-up at six weeks (.0001). Furthermore, the six month post treatment outcomes showed that the veterans in the TLC group had a significant reduction in psychiatric re-hospitalization days (.05), higher functioning on the Global Assessment in Functioning (.0001), and a greater reduction in symptom severity on all of the BASIS-32 subscales (.006, .006, .001 and .002 respectively). Cost-effectiveness data showed that this intervention easily paid for itself.

Conclusion: This study found that the TLC booster intervention increased treatment compliance, improved psychiatric and substance abuse outcomes, and reduced rates of re-hospitalization through intensive stabilization and comprehensive discharge planning. The six-month outcomes are particularly exciting and suggest that the TLC intervention had robust treatment effects well beyond the initial six-week treatment intervention. We are in the process of developing a treatment manual to assist clinicians in transitioning individuals with a persistent mental illness from Acute Psychiatry to outpatient services.

Disclosure: Supported by the Department of Veterans Affairs

POSTER NO. 2

MIDLIFE OUTCOMES OF 100 ADHD BOYS: PREDICTION BY ASPECTS OF TREATMENT WITH METHYLPHENIDATE

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Introduction: These are the first midlife data from the earliest U.S. comprehensive longitudinal study of what is now called Attention-Deficit/Hyperactivity Disorder (ADHD). The focus of this preliminary presentation is on the prediction of midlife outcomes by aspects of childhood treatment with methylphenidate (MPH). These data address the question of whether MPH predisposes ADHD children to long-term negative consequences.

Methods: Boys with ADHD-related problems were referred to the University of Iowa Child Psychiatry Outpatient Clinic between 1967 and 1978. They were treated clinically with Ritalin© for an average of 36 months. The most recent follow-up evaluation was carried out beginning in 2001, when the boys were between 35 and 45 years of age. Selected midlife outcomes of the first 100 participants were predicted in a series of hierarchical multiple regressions, using childhood IQ, childhood symptom dimensions (inattention-overactivity and aggression), and aspects of MPH (initial and long-term responsiveness, cumulative dosage, and duration of treatment) as potential predictors. In each analysis, when an aspect of MPH was evaluated as a predictor, childhood IQ, childhood symptoms, and other aspects of MPH were held constant.

Results: In a previous predictive study at young adulthood (Paternite, Loney, Salisbury, & Whaley, 1999), childhood symptom dimensions and aspects of medication significantly predicted impairment, personality dimensions (MMPI), cognitive and academic scores (WAIS, WRAT), and social functioning. In this midlife predictive study, negative outcomes were again associated with the severity of childhood aggression, and some positive outcomes were associated with treatment, usually with higher cumulative dosages of MPH.

Conclusions: Childhood treatment with MPH appears to have some effects on midlife functioning of 100 subjects more than 30 years after treatment began, and more than 15 years after the last individual terminated treatment. Better responsiveness to MPH, higher cumulative dosages, and longer durations of treatment were almost always associated with positive outcomes, with few indications of lasting negative effects of MPH.

Source of Funding: This and previous follow-up waves were supported by the NIH.

POSTER NO. 3

A CONTROLLED TRIAL OF EXTENDED-RELEASE BUPROPION IN ADULT ADHD

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Objective/Background: To evaluate the efficacy and tolerability of a once-daily preparation of a nonstimulant, extended-release bupropion (bupropion XL), in adults with attention-deficit/hyperactivity disorder (ADHD).

Methods: A multi-site, placebo-controlled, parallel-group, 8-week prospective study of 162 subjects (ages 18-60 years) was undertaken in DSM IV diagnosed adults with all subtypes of ADHD. Subjects were treated with up to 450 mg/d of bupropion XL and were rated on multiple outcomes weekly.

Results: Subjects receiving bupropion XL manifested significant improvement on the primary outcome measure, a reduction of =30% in the ADHD Rating Scale as assessed by investigators, over subjects receiving placebo as early as week 2 ($p = 0.01$), which persisted through week 8 ($p = 0.004$). At endpoint, the self-reported Connors Rating Scale scores revealed that bupropion XL provided sustained benefit throughout the day compared to placebo (morning $p = 0.033$, afternoon $p = 0.004$, and evening $p = 0.024$). Only 5% of subjects discontinued because of adverse effects related to the medication. There was no significant difference between bupropion XL and placebo in the incidence of adverse effects.

Conclusion: Once-daily bupropion XL is an effective and well-tolerated nonstimulant treatment for adults with ADHD.

Source(s) of Funding: GlaxoSmithKline

POSTER NO. 4

SYMPTOM PROFILES OF CHILDREN AND ADOLESCENTS WITH A DIAGNOSIS OF ADHD, BIPOLAR DISORDER, OR A DEPRESSIVE DISORDER

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Background: The purpose of this study was to differentiate between symptomatology of children and adolescents with a diagnosis of attention deficit hyperactivity disorder (ADHD), bipolar disorder (BP), or a depressive disorder (DEP) using the Child Behavior Checklist (CBCL).

Method: Any child (4-18 years old) with one of the following diagnoses (ADHD, BP, comorbid ADHD and bipolar disorder [ADHD + BP], DEP, or comorbid ADHD and a depressive disorder [ADHD + DEP]) upon first entry into the TDMHMR system between 1995 and 2000 were eligible for the study. CBCL total, internalizing, externalizing, and subscale scores were compared between diagnostic groups. CBCL comparisons were conducted using analysis of variance (ANOVA). Demographic variables were compared using non-parametric and parametric statistical tests. All tests were two-tailed and significance was defined as an alpha less than 0.001.

Results: From 1995 to 2000, a total of 34,495 children were identified with the following diagnoses: ADHD (n=16,326), BP (n=927), ADHD + BP (n=465), DEP (n=13,603), and ADHD + DEP (n=3,174). CBCL total scores (range of mean difference of CBCL scores between groups: -0.35 to -5.91), internalizing (-5.96 to -7.05), delinquent behaviors (-0.83 to -4.71), withdrawn (-4.59 to -6.16), thought problems (-0.93 to -5.00), anxious/depressed (-5.16 to -7.44), and somatic complaints (-3.71 to -5.40) were significantly lower for the ADHD group compared to any other diagnostic group. The ADHD group scored significantly lower on externalizing (-2.33 to -5.68), social problems (-2.47 to -5.09), aggressive behaviors (-2.17 to -6.83), and attention problems (-2.25 to -3.09) compared to the ADHD + BP or ADHD + DEP groups. The DEP group scored significantly higher on somatic complaints (mean difference: 4.66) and delinquent behaviors (0.83) subscales compared to the ADHD group.

Conclusion: Children and adolescents with a diagnosis of ADHD scored significantly lower on the CBCL total and 6 subscales compared to those with a diagnosis of BP, DEP, ADHD + BP, or ADHD + DEP. The CBCL was able to differentiate between certain symptomatology of ADHD, bipolar disorder, and depressive disorders. Given the overlap of symptoms associated with these mental conditions, it is important for clinicians to distinguish between diagnoses to ensure appropriate pharmacological treatment.

POSTER NO. 5

CORRELATIONS OF PLASMA DRUG LEVELS AND ADHD RESPONSE IN JUVENILES ON BUPROPION SR

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Objective: To explore correlations at steady state between pharmacokinetic (PK) variables and clinical response in youths with attention deficit hyperactivity disorders (ADHD) treated with bupropion SR.

Methods: Subjects (Ss) were 9 boys and 7 girls (mean age: 15.1 + 2.0 yrs) prescribed bupropion SR for ADHD, including inattentive (n=7) and combined (n=9) subtypes. Thirteen also had comorbid depressive disorders, either Major Depression (n=4) or Depressive Disorder NOS (n=9). All took bupropion SR in morning daily doses of 100 mg (n=10) or 200 mg (n=6) for 14 days (mean duration: 28 + 25 days). Data are included twice for 4 Ss studied at both doses. Ss were evaluated for 24 hrs in an inpatient PK lab with serial blood draws from an IV port every 1-3 hours. Plasma concentrations of bupropion (BUP) and its metabolites hydroxybupropion (HB), threohydrobupropion (TB), and erythrohydrobupropion (EB), were examined at intervals 1 to 24 hrs (C1 to C24) after morning doses to determine areas under the concentration curves to infinity (AUC). ADHD response was rated by the study psychiatrist on the Clinician's Global Impression's Improvement scale (CGI-I) (1 = very much improved to 7 = very much worse) blinded to individual subjects' PK data, in order to explore potential correlations with blood levels of BUP and metabolites.

Results: Significant correlations were noted between ADHD response and AUC for BUP (rho = -0.65, p=.007), HB (rho = -0.66, p=.005), EB (rho = -0.61, p=.012), and TB (rho = -0.54, p=.030), along with C7.5 for BUP and all metabolites (all rhos > -.60, all p values < .02). Receiver Operator Characteristic curves analysis identified optimally sensitive and specific cutpoints for BUP and metabolites at 7.5 hours to differentiate the 5 ADHD responders (CGI-I < 2) from the 11 non-responders. Using Fisher's Exact tests, clinical response occurred more frequently in Ss who had BUP levels > 40 ng/ml (p=.03), HB levels > 600 ng/ml (p=.01), TB levels > 240 ng/ml (p=.11), or EB levels > 45 ng/ml (p=.03) at 7.5 hours.

Conclusions: In ADHD youths treated with bupropion SR, BUP and metabolite levels at 7.5 hours after morning doses may correlate with ADHD response, pending confirmation of these findings in an independent sample under placebo-controlled, double-blinded conditions.

Sources of Funding: NIMH grants N01 MH070008, P30 MH055123, and K23 MH065375.

POSTER NO. 6

SAFETY AND EFFECTIVENESS OF OROS MPH AND ATOMOXETINE

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Background: Compare safety and effectiveness of OROS MPH and atomoxetine in children with Attention-deficit/hyperactivity disorder (ADHD).

Methods: Prospective, randomized (2:1), open-label, 3-week study of OROS MPH and atomoxetine in ADHD children ages 6-12. Patients were newly diagnosed or sub-optimally managed on current treatment and had an Attention Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) score $\geq$24 and a Clinical Global Impressions-Severity of Illness (CGI-S) score >3. Medication was initiated and titrated based on the investigator's clinical judgment in accordance with each product's package insert. Investigators rated improvement via the ADHD-RS at weekly visits.

Results: To date, 651 subjects have completed the study (OROS MPH, n=422; atomoxetine, n=229). Baseline ADHD-RS scores were similar in the OROS MPH and atomoxetine groups (39.77 vs. 38.87). OROS® MPH patients had significantly greater improvement in the investigator-evaluated ADHD-RS score than atomoxetine patients at visit 1 (mean difference: 2.95; mean change from baseline: 11.50 vs. 8.55; $p<0.0006$), visit 2 (mean difference: 3.68; mean change from baseline: 16.17 vs. 12.49; $p<0.0001$), and visit 3 (mean difference: 5.16; mean change from baseline 21.10 vs. 15.94; $p<0.0001$). Response rates ($\geq$25% reduction from baseline on ADHD-RS) at visit 3 were greater for OROS MPH vs. atomoxetine (82.7% vs. 67.3%; $p<0.0001$). Rates of adverse events were similar in both treatment groups.

Conclusions: Preliminary results from this direct comparison demonstrate significantly greater symptom improvement with OROS MPH versus atomoxetine at weeks one, two, and three. Response rates were also greater with OROS MPH. Rates of adverse events were similar.

Source of Funding: McNeil Consumer & Specialty Pharmaceuticals

POSTER NO. 7

ADHERENCE MEASURES OF PSYCHOSTIMULANTS USED IN THE TREATMENT OF ADHD IN CHILDREN AND ADOLESCENTS

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Objective/Background: The purpose of this study was to examine adherence measures of different psychostimulants in school-aged children with ADHD.

Methods: Paid prescription claims for new stimulant medication starts during the 2001-2002 school year were extracted from the Texas Medicaid prescription claims database. Adherence measures examined over a six-month treatment period included persistence and medication possession ratio (MPR). Adherence was evaluated based on drug, age, and gender.

Results: A total of 28,344 prescriptions representing 9,549 patients were available for analysis. Persistence was greater for methylphenidate extended release (MER, Concerta) (0.50) than for mixed amphetamine salts (MAS) (0.42) or methylphenidate immediate release (MIR) (0.37), $p < 0.001$. MPR was also greater for MER (0.76) than for MAS (0.73) or MPH (0.69), $p < 0.001$. Subjects ages 5-9 exhibited better persistence and MPR than those ages 10-14 and 15-18, $p < 0.001$ No gender-related differences in adherence were observed.

Conclusion: Although adherence measures were significantly better for MER than compared stimulants, the clinical meaningfulness of these differences cannot be definitely concluded from these data. Further research into pharmaceutical products, administration methods, and clinical interventions that may enhance adherence should be conducted.

Source(s) of Funding: None

POSTER NO. 8

SAFETY PROFILE OF BUPROPION SR IN CHILDREN: A RETROSPECTIVE CHART REVIEW

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Objective/Background: There has been a large increase in the use of antidepressant medications in children for a variety of conditions including the treatment of attention deficit/hyperactivity disorder (ADHD) with limited information available pertaining to the side effects when dealing with children. It is important to psychiatrists contemplating administering antidepressants to their child patients, to have more information about their safety profile. Patients and their parents also need this information. The goal of this investigation was to determine the frequency and seriousness of the side effects when Bupropion SR (WBSR) was prescribed to children aged six to twelve.

Methods: This study examined charts of patients seen for psychopharmacological treatment at a child psychiatry private practice. This study was conducted by a thorough retrospective examination of clinical records of all children aged six to twelve. All patients meeting the criteria were included in the chart review. Due to the known risk of seizure, children identified during the clinical review as bulimic, having a history of head injuries or seizures would not be prescribed WBSR. Clinical records included the psychiatrist's detailed notes of side effects reported by patients during open-ended questioning at regularly scheduled medication management sessions.

Results: 867 charts were reviewed of children born between 1986-1996 at an out patient psychopharmacological clinic. Out of all charts examined, 285 patients were administered WBSR at some point. There were 201 males and 84 females in this review, the children were M=9.98, SD=1.84 years in age, and mean weight of M=83.8, SD=29.36 pounds. Patients received WBSR for M=13.05, SD=12.04 months. Twenty-three patients discontinued using WBSR within the first month. Patients that discontinued the use of WBSR due to experiencing side effects was 5.6 percent. Four patients experienced seizures while on WBSR; three discontinued the medication immediately following the episode. No other significant side effects were identified during the review. Thirty-nine percent of the patients reported no side effects what so ever while being administered WBSR. One quarter of patients reported initial insomnia, fourteen percent reported a decrease in appetite, and approximately six percent reported headaches, and upset stomach or nausea.

Conclusion: WBSR is generally well tolerated in children aged 6-12 years old. There was approximately a one percent risk of seizures in the 285 children who were administered WBSR for an average of thirteen months. No other serious side effects emerged. The study is limited by its nature as a retrospective chart review.

Source(s) of Funding: No outside source of funding was utilized for this investigation.

POSTER NO. 9

MODAFINIL AS THERAPY FOR ADHD IN CHILDREN: AN 8-WEEK, OPEN-LABEL STUDY

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Objective/Background: Attention deficit/hyperactivity disorder (ADHD) is estimated to affect 8% to 10% of school-aged children. Characteristic behaviors include developmentally inappropriate inattention, impulsivity, and hyperactivity. The most commonly prescribed medications for the treatment of pediatric ADHD are the stimulant drugs methylphenidate and amphetamine. Although these agents are effective in managing core symptoms in many patients with ADHD, 20% to 40% of patients do not respond adequately or are unable to tolerate these drugs. The stimulants may also be limited by their potential for abuse. Modafinil is a novel wake-promoting agent that has a relatively low risk of abuse. In a 4-week, double-blind, placebo-controlled study, modafinil significantly improved ADHD symptoms in children and adolescents and was well tolerated. This study assessed the continued efficacy and tolerability of modafinil for an additional 8 weeks.

Methods: This 8-week, open-label follow-up study enrolled 220 patients (age range, 6-14 yr) with ADHD, who completed the prior double-blind study or discontinued for reasons other than adverse events. Treatment with modafinil started at 100 mg/day administered once in the morning and was titrated based on clinical effect and tolerability. The maximum dosage to be administered was 500 mg/day (divided dose, morning and midday). The 8 weeks of treatment were continuous from the double-blind treatment period, ie, first week of open-label treatment was week 5. Efficacy assessments included the ADHD Rating Scale IV (clinician), Conners' ADHD/DSM-IV Scale-parent (CADS-P), and Clinical Global Impression of Change (CGI-C, clinician).

Results: 166 of 220 patients (75%) completed the study. Modafinil improved ADHD symptoms on all rating scales and subscales during open-label treatment, in a manner consistent with significant improvements obtained with modafinil during double-blind treatment. On the ADHD Rating Scale-IV (clinician-rated home version), modafinil improved scores on the total, inattention, and hyperactivity/impulsivity subscales at endpoint ($p<0.001$ vs baseline). On the CADS-P, modafinil improved scores on the ADHD index and total and inattention subscales ($p<0.001$ vs baseline) and on the hyperactivity/impulsivity subscale ($p<0.01$ vs baseline). Improvement in overall clinical condition was seen at the first 2 weeks of the open-label phase and continued throughout the open-label period, with 76% of children showing improvement at endpoint. Modafinil was well tolerated. The most common adverse events were insomnia (13%) and headache (10%).

Conclusion: Over the course of this 8-week follow-up, modafinil continued to be an effective and well-tolerated therapy for improving symptoms and overall clinical status of children with ADHD.

Source(s) of Funding: Cephalon, Inc., West Chester, PA

POSTER NO. 10

A COHORT ANALYSIS OF MEASURED GROWTH PARAMETERS IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER RECEIVING MIXED AMPHETAMINE SALTS (MAS XR) FOR 24 MONTHS

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Objective/Background: To compare the actual growth (height and weight) observed in children with ADHD receiving MAS XR for 24 months to the published CDC norms for the respective age groups.

Methods: To be considered for this analysis, children in the long-term, open-label safety-extension trial of MAS XR had to have at least 14 evaluable (baseline and monthly for months 12-24) measures of growth (height and weight). If a value(s) was missing or not recorded for a particular month(s), the value of the immediately preceding visit was carried forward unchanged. Subjects were then stratified into cohorts by age of entry into the study, then again by sex. Mean and actual heights and weights were plotted for all cohorts. The current CDC growth charts were obtained and values for the 50th percentile for height and weight for the corresponding age cohorts were plotted for comparison.

Results: At the conclusion of the 24-month study, the mean childrens' height increased an average of 3.75 inches while their weight increased an average 11.02 lbs. Male and female children with 14 evaluable measures of height grew an average of 3.98 and 3.61 inches respectively and in the majority of cases this growth tracked above or on par with 50th percentile CDC growth charts.

Conclusion: Despite losses in expected growth that show some catch-up in the second year, actual growth, measured in height and weight over time, shows consistent measurable increases over a 24-month period in children receiving MAS XR for ADHD. Clinicians should monitor the growth of children on ADHD medications individually and make adjustments in therapy only as indicated. In addition, investigation into the use of biological parental height as an estimate of true predicted growth is warranted.

Source(s) of Funding: Shire Pharmaceutical Development Inc.

POSTER NO. 11

ADHD SYMPTOM RESPONSE AND REMISSION AS A FUNCTION OF STIMULANT THERAPY DOSAGE

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Objective/Background: To examine symptom response and remission as a function of dosage in children with attention-deficit/hyperactivity disorder (ADHD) treated with methylphenidate (MPH).

Methods: Children with ADHD (N=282), ages 6-12 years, were randomized to once-daily OROS MPH (CONCERTA, 18mg-54mg, n=95), immediate-release (IR) MPH three times a day (tid; 5mg-15mg, n=97), or placebo (n=90) in a double-blind, 28-day trial. Patients were assigned to treatment dose levels based either on titration or conversion from previous MPH. Symptom response and remission rates at end of study (>=30% and >=50% reduction from baseline on parent-rated IOWA Conners inattention/overactivity (I/O) subscale, respectively) were retrospectively analyzed using the last-observation-carried forward (LOCF) procedure.

Results: Response rates were 69.2% for OROS MPH, 61.1% for IR MPH, and 21.4% for placebo (P<0.0001). These rates were 83.6% and 40% for OROS MPH dosages 36-54mg and 18mg, respectively (P=0.0001). Remission rates were 50.5% for OROS MPH, 36.7% for IR MPH, and 11.9% for placebo (P<0.0001). These rates were 62.3% and 26.7% for OROS MPH dosages 36-54mg and 18mg, respectively (P=0.0018). No significant differences in response and remission rates were observed for IR MPH by dosage.

Conclusion: Significantly more patients achieved criteria for symptom response and remission of ADHD symptoms when treated with once-daily OROS MPH than with placebo. Response and remission rates were numerically higher with OROS MPH versus IR MPH. Significantly higher response and remission rates were achieved with higher doses of OROS MPH.

Source(s) of Funding: McNeil Consumer & Specialty Pharmaceuticals

POSTER NO. 12

PHARMACOKINETICS OF AN EXTENDED-RELEASE FORMULATION OF MIXED AMPHETAMINE SALTS (MAS XR) IN ADOLESCENTS WITH ADHD

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Objective/Background: Attention-deficit/hyperactivity disorder (ADHD) may persist into adolescence and adulthood in up to 80% of children diagnosed with the disorder. Published data indicate that short-acting stimulants are effective in treating both children and adolescents with ADHD. The objective of this study was to evaluate the pharmacokinetic variables of single, oral doses of 10, 20, 40, or 60 mg of an extended-release formulation of mixed amphetamine salts (MAS XR; Adderall XR®) in adolescents with ADHD.

Methods: This study was an open-label, single-dose, randomized, 3-way crossover design. Adolescents aged 13 to 17 years with ADHD weighing <=75 kg (165 lbs) were randomized to received single oral doses of 10, 20, and 40 mg MAS XR in randomized order with a 1-week washout between each of the 3 doses. Adolescents weighing >75 kg were randomized to received single oral doses of 20, 40, and 60 mg in randomized order with a 1-week washout between each dose. Blood samples were taken from each subject before each dose and hourly up to 12 hours postdose, and at 14, 16, 24, 36, 48, and 60 hours postdose. Blood pressure and pulse were assessed before each dose and 2, 4, 24, and 60 postdose. Plasma d- and l-amphetamine were assayed using a validated LC/MS/MS method. The effects of age, gender, and body weight on the pharmacokinetic variables also will be analyzed.

Results: In adolescents weighing <=75 kg, the $AUC_{0\text{-}inf}$ values (mean ± SD) for d-amphetamine were 351 ± 57.1, 689 ± 128, and 1426 ± 285 ng·hr/mL for the 10, 20, and 40 mg doses, respectively. The corresponding mean C_{max} values were 18.4 ± 2.96, 34.1 ± 7.8, and 69.6 ± 15.17 ng/mL. In adolescents weighing >75 kg, the $AUC_{0\text{-}inf}$ values (mean ± SD) for d-amphetamine were 589 ± 84.3, 1177 ± 204, and 1999 ± 366 ng·hr/mL for the 20, 40, and 60 mg doses, respectively. The corresponding mean C_{max} values were 29.4 ± 2.7, 60.7 ± 5.91, 81.6 ± 9.16 ng/mL. Mean $AUC_{0\text{-}inf}$ and C_{max} values for l-amphetamine were approximately 1/3 those of d-amphetamine for each of the doses within each weight group.

Conclusion: For each weight group, exposure to d- and l-amphetamine as quantified by PK variables of $AUC_{0\text{-}inf}$ and Cmax was linear and directly related to the quantity of drug administered following a single, oral dose of MAS XR 10, 20, 40, or 60 mg in adolescents.

Source(s) of Funding: Supported by Shire Pharmaceutical Development Inc.

POSTER NO. 13

THE EFFECTS OF GINKGO BILOBA ON MEMORY IN HEALTHY MIDDLE-AGED VOLUNTEERS

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Objective/Background: Despite a large body of evidence supporting the beneficial effects of ginkgo biloba on various actions of cognitive function in normals and impaired populations, a recent trial which failed to find positive effects of a standardised extract of ginkgo on memory in healthy elderly volunteers using a variety of traditional assessment techniques has received considerable publicity (Solomon et al, 2002, Ginkgo for memory enhancement, JAMA 288: 835-840). The present study evaluated the same extract using a widely used automated cognitive test system specifically designed for use in clinical trials.

Methods: This was a randomised, double-blind, placebo controlled, 8 week study of the effects of the standardised ginkgo extract GK501 on the cognitive function of 120 healthy adults aged 40 to 60 years. The Cognitive Drug Research (CDR) computersied assessment system was used to test a range of aspects of cognitive function including attention, working memory and episodic secondary memory. Following four pre-study training sessions on the CDR system the volunteers were tested at pre-dose, 2, 4 and 6 hours post-dosing on day 1, day 28 and day 56. In addition three traditional tests were administer once pre-dose and once at 8 weeks (Stroop, Trails and Buschke Selective Reminding).

Results: The most consistent effect was improved episodic secondary memory seen on the Quality of Episodic Memory factor score from the CDR system. This significant enhancement peaked in relation to placebo at day 28. There were no clear effects on attention or working memory with GK501. No benefits were seen on the traditional tests.

Conclusion: This study has provided evidence that GK501 can enhance memory in cognitively intact middle aged volunteers. The magnitude of the benefit is comparable to that seen in this population on the same test system with a combination of GK501 and ginseng (Wesnes et al, 2000, The memory enhancing effects of a Ginkgo biloba/Panax ginseng combination in healthy middle aged volunteers. Psychopharmacology 152: 353-361). Besides the advantages of using test systems specifically designed for use in clinical trials, the repetition of testing over the study day has been a consistent feature in this and a range of related trials identifying enhancement in normal volunteers with a variety of substances (eg ginkgo, ginseng, sage, and Melissa).

Source(s) of Funding: This study was supported by Pharmaton SA, Lugano, Switzerland.

POSTER NO. 14

AN ACADEMIC SPECIALTY CLINIC-BASED COMPARISON OF NEXT-STEP SWITCHING VERSUS AUGMENTATION STRATEGIES IN OUTPATIENTS WITH MAJOR DEPRESSIVE DISORDER RESISTANT TO A SINGLE ANTIDEPRESSANT TRIAL

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Objective/Background: Whether it is preferable to augment or switch the antidepressant regimen among patients with Major Depressive Disorder (MDD) who have had some versus no symptom improvement remains unclear.

Methods: 85 outpatients who had not received antidepressant treatment for the current major depressive episode (MDE) prior to enrollment in one of two specialty clinics, and who had not achieved remission after a first adequate prospective antidepressant trial conducted at the clinic underwent either augmentation (n=36) or switching (n=49) of their antidepressant regimen. Outcome was defined with the use of the Clinical Global Impressions (CGI) Scale.

Results: Nonresponders (CGI-I>3) were more likely to have their treatment switched than patients who experienced incomplete response (CGI-I<4, CGI-S>1) (67.2% versus 28.5%, p=0.001). Incomplete responders during the first trial that went on to receive augmentation had higher remission rates (60.0% versus 0%, p=0.01), lower endpoint depression severity scores (1.8 ± 1.1 versus 3.3 ± 0.8, p=0.01) and greater clinical improvement scores (1.6 ± 1.1 versus 3.0 ± 0.0, p=0.03) than incomplete responders who had their antidepressant regimen switched. Although nonresponders to the first treatment who were switched experienced greater symptom improvement than nonresponders who were augmented (2.7 ± 1.1 versus 3.4 ± 1.2, p=0.03), there was no significant difference (p>0.05) between these two groups with respect to remission rates (18.6% versus 14.2%, respectively) and endpoint depressive severity (3.0 ± 1.4 versus 3.4 ± 1.4, respectively).

Conclusion: In this naturalistic treatment setting, nonresponders during their first adequate antidepressant trial were more likely to have their antidepressant regimen switched, while patients with incomplete response during the first trial were more likely to have their regimen augmented. In addition, patients with incomplete response who had their treatment augmented had better outcome than patients with incomplete response who had their treatment switched.

Source(s) of Funding: Supported by the American College of Neuropsychopharmacology (ACNP)/ GlaxoSmithKline (GSK) Fellowship in Clinical Neuropsychopharmacology (GIP).

POSTER NO. 15

MODAFINIL AS POTENTIAL TREATMENT FOR COCAINE DEPENDENCE

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Objective/Background: The 2002 National Survey on Drug Use and Health estimates that 2 million Americans (0.9%) aged 12 or older are cocaine users. Ideally, a pharmacologic therapy for cocaine addiction should have limited abuse potential, ameliorate abstinence syndrome, suppress cocaine use, and have a favorable safety and pharmacokinetic profile. The wake-promoting agent modafinil selectively modulates hypothalamocortical pathways involved in the regulation of normal wakefulness and has lower discrimination and reinforcing properties than CNS stimulants. Preliminary data indicate that modafinil reverses cocaine withdrawal symptoms within hours. This study evaluated the efficacy and safety/pharmacokinetic profile of modafinil as potential treatment for cocaine dependence.

Methods: A safety/pharmacokinetic interaction study between intravenous (IV) cocaine and steady-state oral modafinil was conducted in non-treatment-seeking subjects with cocaine dependence. In double-blind fashion, cocaine (20 mg or 40 mg) or saline was administered intravenously over 1 minute. Modafinil (200 mg twice daily for 7 days followed by 400 mg twice daily for 7 days) was administered open-label. Subjective visual analog scale (VAS) measures of "any drug effect," "cocaine high," and "amount willing to pay" were assessed, and pharmacokinetic interactions between cocaine and modafinil were determined. Tolerability and safety assessments included blood pressure/heart rate, adverse events, clinical laboratory parameters, and behavioral/psychiatric toxicities.

Results: 12 inpatients (mean[±SD] age=33±10 years) were included in the study; subjects had a mean cocaine use of 11±8 years. Modafinil (400 and 800 mg/day) significantly reduced cocaine euphoria as assessed using VAS measures of "any drug effect," "cocaine high," and "amount willing to pay" ($p<.017$). Modafinil caused no increase in plasma concentrations of cocaine versus baseline and no inhibition of cocaine elimination. Modafinil steady-state caused no increase in systolic/diastolic blood pressure or heart rate (at either dose of modafinil or cocaine). Modafinil (400 and 800 mg/day) significantly reduced peak systolic pressure caused by cocaine (20 or 40 mg IV). The most common adverse events were headache (n=10, 83%), insomnia (n=9, 75%), dyspepsia (n=4, 33%), and nasal congestion (n=4, 33%). Modafinil had no clinically meaningful effects on clinical laboratory parameters and was not associated with behavioral/psychiatric toxicities.

Conclusion: Modafinil demonstrated positive effects in reducing cocaine euphoria, suggesting it may be an effective medication for cocaine dependence. Modafinil was well tolerated.

Source(s) of Funding: Clinical Trial Operations, NIDA, NIH Contract #DA98102

POSTER NO. 16

COMPARISON OF LONG-ACTING METHYLPHENIDATE FORMULATIONS IN CHILDREN WITH ADHD: POOLED ANALYSIS OF 2 RANDOMIZED, PLACEBO-CONTROLLED STUDIES

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Background: Preliminary studies have shown significant differences in efficacy between once-daily formulations of methylphenidate (MPH). The objective of this supplemental analysis is to better characterize the differences in response patterns over 8 hours by pooling data from 2 similarly designed studies in children with attention-deficit/hyperactivity disorder (ADHD).

Method: In 2 single-blind, crossover studies, children with ADHD were randomized to sequentially receive (at weekly intervals) 20 mg extended-release MPH capsules (ER-MPH; Ritalin® LA™), 18-mg or 36 mg modified-release MPH tablets (MR-MPH; Concerta®), and placebo. Efficacy was assessed in a laboratory classroom from 0.5 through 8 hours postdose using the SKAMP ratings (Attention and Deportment subscales) and the number of math problems attempted and correctly answered on written tests. Efficacy was evaluated in 55 children aged 6 to 12 years who had previously been stabilized on the equivalence of 20-mg immediate-release MPH daily.

Results: The change from predose in SKAMP-Attention score was significantly greater with ER-MPH 20 mg than with one or both doses of MR-MPH at all time points up to 6 hours ($P<.05$), and all active treatments were equivalent at 8 hours. The change from predose in SKAMP-Deportment score showed a significant advantage of ER-MPH 20 mg over each dose of MR-MPH at all time points from 0.5 to 3 hours ($P<.05$), as well as superiority to MR-MPH 18 mg at 6 hours ($P<.05$). The number of math test problems attempted also showed that ER MPH 20 mg was more effective than each dose of MR-MPH in the morning ($P<.05$ vs MR MPH 36 mg from 0.5 through 2 hours, and $P<.05$ vs MR-MPH 18 mg at 3 and 4 hours) and was equivalent to them in the afternoon. Similarly, math problems correctly answered demonstrated consistently greater improvements with ER-MPH 20 mg than with MR-MPH; at all time points up to 6 hours, the differences were significant compared with either MR-MPH 18 mg or 36 mg. Neither dose of MR-MPH outperformed ER-MPH 20 mg at any time point on any of the efficacy variables examined.

Conclusion: The differences in the way these 2 preparations deliver MPH yield meaningful differences in behavioral control for the samples examined over the course of the school day.

Source of Funding: This study was supported by Novartis Pharmaceuticals Corporation.

POSTER NO. 17

A PRELIMINARY CONTROLLED TRIAL OF DIVALPROEX IN PTSD

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Background/Objective: The standard of care for chronic PTSD involves the combination of psychotherapy and antidepressant medication. However, many patients do not have an adequate treatment response to antidepressants. Therefore, other classes of psychotropics have been utilized. There have been several open trials of divalaproex in PTSD and this and other mood-stabilizers are often utilized alone or as aduncts. The objective of this study was to conduct a placebo controlled study of the efficacy and tolerability of divalproex in chronic PTSD patients.

Method: A ten week, prospective, double-blind, placebo-controlled trial was conducted in patients recruited from our VA PTSD clinic. Patients met DSM-IV criteria for PTSD based on SCID and Clinician Administered PTSD scale (CAPS diagnostic version) interviews. After a one week placebo lead-in phase, patients were randomized to receive placebo or divalproex. Divalproex was initiated at a dose of 750 mg daily and titrated to obtain blood levels between 50 and 125 ug/ml. Concomitant psychiatric medications, except mood-stabilizers, were permitted if their dose(s) was held constant for 4 weeks prior to study entry and during the study. The primary outcome variable was the CAPS, change version, with several secondary measures also obtained.

Results: Twenty-nine patients were randomized, 16 received divalproex and 13 received placebo. There were no significant differences between groups (divalproex versus placebo) in mean change from baseline to endpoint (LOCF) on the total CAPS scores or in subscale scores except for lower avoidance/numbing scores with placebo versus divalproex. Although several patients appeared to be responders to divalproex, this clinical observation was not reflected in the between group differences. Divalproex was well tolerated with no serious adverse events.

Conclusion: Responses to divalproex in PTSD global (CAPS) ratings did not differ between divalproex and placebo in this preliminary controlled study. This could be due to lack of efficacy of divalproex, inadequate sample size to detect differences, patient selection for this treatment, or other factors. Further study of divalproex and other mood stabilizers is needed to better clarify the role of these agents in PTSD.

Funding: Abbott Laboratories (investigator-initiated study)

POSTER NO. 18

EFFICACY OF DEXMETHYLPHENIDATE EXTENDED-RELEASE CAPSULES IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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Background: Dexmethylphenidate is the pharmacologically active d threo enantiomer of methylphenidate. Efficacy of once-daily dexmethylphenidate extended-release (d-MPH-ER) capsules versus placebo was evaluated in adults with attention-deficit/hyperactivity disorder (ADHD).

Methods: In a multicenter, double-blind, parallel-group, placebo-controlled study, 221 adults diagnosed with ADHD and childhood onset of ADHD were randomized; 184 patients completed. Following a 1-week screening period, patients were randomized to 1 of 4 treatments: d-MPH-ER 20 mg, 30 mg, 40 mg, or placebo once daily for 5 weeks. The primary efficacy variable was the change in DSM-IV ADHD Rating Scale total scores at final visit compared with baseline. Secondary parameters included assessment of the Clinical Global Impression score for Improvement (CGI-I).

Results: At final visit, mean change from baseline in DSM-IV Rating Scale was 7.9 for placebo, 13.7 for d MPH ER 20 mg (P=.006), 13.4 for d-MPH-ER 30 mg (P=.012), and 16.9 (P<.001) for d-MPH-ER 40 mg (all P values are versus placebo). When the 2 subscales of the DSM-IV Rating Scale were analyzed, results were significant for both Inattentive and Hyperactive/Impulsivity subscales for all treatment groups. At final visit, mean change from baseline for Inattentive subscale was 4.7 for placebo, 7.7 for d MPH ER 20 mg (P=.021), 8.0 for d-MPH-ER 30 mg (P=.011), and 9.7 (P<.001) for d-MPH-ER 40 mg. For the Hyperactive/Impulsivity subscale mean change from baseline was 3.2 for placebo, 6.0 for d MPH ER 20 mg (P=.005), 5.4 for d MPH-ER 30 mg (P=.037), and 7.2 (P<.001) for d-MPH ER 40 mg.

The proportion of patients with =30% improvement on the DSM-IV Rating Scale total score at final visit was 34.0% for placebo, 57.9% for d-MPH-ER 20 mg (P=.017), 53.7% for d-MPH-ER 30 mg (P=.054), and 61.1% for d-MPH-ER 40 mg (P=.007). Additionally, CGI-ratings at final visit were compared between each of the d-MPH-ER groups. The percentage of patients with improvement (ie, score of 1 [very much improved] or 2 [much improved]) on the CGI-I at final visit was 26.4% for placebo, 47.4% for d-MPH-ER 20 mg (P=.027), 37.0% for d-MPH-ER 30 mg (P=.261), and 55.6% for d-MPH-ER 40 mg (P=.003). Safety and tolerability were consistent with immediate-release d-MPH and MPH.

Conclusion: In once-daily doses of 20 mg, 30 mg, or 40 mg, d-MPH-ER is a safe and effective treatment for adult patients with ADHD, as demonstrated by the assessment of ADHD symptoms.

Source of Funding: This study was supported by Novartis Pharmaceuticals Corporation.

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POSTER NO. 19

RISPERIDONE FOR THE TREATMENT OF REFRACTORY PANIC, SOCIAL ANXIETY AND GENERALIZED ANXIETY DISORDERS

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Objective/Background: Evidence supporting a role for atypical antipsychotics, such as risperidone, as augmentation tools for refractory anxiety disorders is emerging.

Methods: Fifteen patients (40% women; mean age = 40 years) with generalized anxiety disorder (GAD), panic disorder (PD), or social anxiety disorder (SAD), who remained symptomatic despite at least 8 weeks of pharmacotherapy at an adequate (or highest tolerated) dose of an antidepressant or benzodiazepine received risperidone initiated at 0.25 mg/day and flexibly titrated over 8 weeks. The primary outcome measure was the Clinical Global Impression- Severity Scale (CGI-S), with secondary disorder specific ratings.

Results: Open treatment with adjunctive risperidone at a mean dose of 1.5mg/d +/- 0.87 resulted in significant improvement on the CGI-S for all patients ($p<0.001$; mean reduction=1.5 points) and a significant reduction on the HAM-A for those with GAD ($p<0.02$; mean change = 6.9 points). Risperidone was generally well tolerated, with 2 discontinuations due to sedation and weight gain, respectively. The most common side effects included sedation, dry mouth, and increased appetite and/or weight gain. There was no increase in extrapyramidal (EPS) ratings.

Conclusion: Risperidone may be a safe and effective augmentation strategy for GAD, SAD and PD, with evaluation in larger, controlled study warranted.

Source(s) of Funding: Janssen Pharmaceutica Products LP

POSTER NO. 20

THE IMPACT OF AFFECTIVE SYMPTOMATOLOGY ON THE MULTIMODAL TREATMENT OF PEDIATRIC ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

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Objective/Background: There is growing evidence that children with ADHD manifest elevated rates of affective illness. It is unclear how children with depressive or manic symptoms respond to ADHD treatments and how ADHD treatments impact mood. This study examines the tolerability and efficacy of multimodal treatment for ADHD in children with comorbid affective symptomatology.

Methods: Subjects were recruited from a randomized, double-blind, crossover study of methylphenidate (MPH) (.45-1.8mg/kg per day) and behavior modification (BMOD) in children ages 5-12 with ADHD set at a therapeutic summer-camp (NIMH #MH62946: PI William Pelham). All camp participants were screened for affective symptoms to identify a subgroup that may exhibit differential responses to ADHD interventions. Those with elevated Young Mania Rating Scale (YMRS >12) or Children's Depression Rating Scale- Revised (CDRS-R >30) scores underwent weekly mood assessments, in addition to daily ADHD measures. 20 subjects were identified: 2 with depressive symptoms, 7 with manic and 11 with symptoms of both. Primary outcome measures of mood were: clinician and parent YMRS, CDRS-R and Clinical Global Improvement Scale (CGI). ADHD outcome measures were: objective frequency counts of externalizing behaviors during camp, IOWA Conners and CGI.

Results: 19 (95%) subjects completed all 9 weeks. 17 (85%) subjects demonstrated significant improvement in ADHD symptoms (CGI-Improvement much/very much). MPH and BMOD were both rated as efficacious, although 50% of subjects required the highest MPH dose to achieve maximal response. There was no significant difference between groups (mood/no-mood) for improvement of ADHD symptoms on any measure. Parents, but not camp staff, rated the mood group as more oppositional/aggressive pre (IOWA Conners: t stat -2.82, p<.001) and post treatment (t stat -2.86, p<.001) and more globally impaired (t stat -4.76, p<.001) post treatment. Increasing MPH doses were not associated with worsening manic symptoms, as MPH was generally well tolerated. Multimodal treatment was associated with significant reductions in YMRS (-30%, t Stat 6.7, p<.001) and CDRS scores (-30%, t Stat 6.9, p<.001). 14/18 (78%) subjects with manic and 10/13 (77%) with depressive symptoms demonstrated significant improvement in mood (CGI-Improvement much/very much).

Conclusion: Results suggest that affective symptoms do not significantly moderate treatment response for pediatric ADHD but may be associated with greater oppositional symptoms and impairment at home. Multimodal treatment was associated with improvements, not worsening, in mood. Therefore, in children with ADHD and subthreshold affective illness, MPH and BMOD appear to be safe and effective treatments.

Source(s) of Funding: Funding for this project was provided by the Klingenstein Third Generation Foundation while the 2003 Summer Treatment Program was funded by NIMH grant # MH62946 (PI: William Pelham).

POSTER NO. 21

EFFECTS OF TREATMENT WITH LY354740, LORAZEPAM, OR PLACEBO IN PATIENTS WITH A PRIMARY DIAGNOSIS OF GENERALIZED ANXIETY DISORDER

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Objective/Background: L-Glutamate (glutamate) is a major excitatory neurotransmitter in most CNS processes. Glutamate-stimulated, fast synaptic transmission is modulated via metabotropic receptors (mGlus). mGlu2/3 receptors play an important role in somatic expression of fear via the brain stem/spinal cord. LY354740 is a structural analogue of glutamate with specificity for mGlu2/3 receptors. LY354740 has shown anxiolytic properties in laboratory animals and in human models of anxiety including fear potentiated startle and CO2-incduced panic anxiety. This study compares the effects of treatment with LY354740 100 mg BID, LY354740 200 mg BID, lorazepam 4-5 mg/day or placebo, on symptoms of generalized anxiety disorder (GAD).

Methods: Inclusion criteria for this study included a principal diagnosis of GAD (DSM-IV), HAMA score $\geq$20 and a score $\geq$2 on both HAMA item 1 (anxious mood) and item 2 (tension). Patients (N=738) were randomized to double-blind treatment with fixed doses of LY354740 100 mg BID (n=201), LY354740 200 mg BID (n=201), lorazepam (n=134), and placebo (n=202). The study employed a double-blind placebo lead-in period and a double-blind drug discontinuation/taper period.

Results: After 5 weeks of treatment, LY354740 100 mg BID, LY354740 200 mg BID, and lorazepam were all associated with significantly greater mean change in HAMA total score compared with placebo (LY 100 -10.01; LY 200 -9.80; LRZ -10.36; PLC -8.03; all p-values $\leq$0.004). Response was defined as a decrease of 50% or more in HAMA total score for the subset of patients treated for a minimum of 10 days. Statistically significantly more LY354740- and lorazepam-treated patients were classified as responders compared to placebo-treated patients (LY 100 49%; LY 200 52%; LRZ 53%; PLC 36%; all p-values $\leq$0.007). Significantly greater improvements for all active treatment groups compared with placebo were also observed for HADS anxiety subscale score and CGI-Severity, as well as the HAMA psychic and somatic subscores. LY354740 treatment was not associated with any adverse event at a statistically greater frequency than placebo. Compared with either LY354740 regimen, lorazepam was associated with significantly more treatment-emergent somnolence, dizziness, disturbance in attention, muscle weakness, and coordination abnormalities (all p-values£0.040). Additionally, neither dosage of LY354740 was associated with withdrawal symptoms. Lorazepam was associated with significantly more withdrawal than placebo or either LY354740 treatment regimen (p<.05 vs. all groups) as evidenced by worsening on the HAMA total score, HAMA psychic and somatic factor scores and the HADS anxiety subscale score.

Conclusion: LY354740 100 BID and LY354740 200 BID are effective and well-tolerated for acute treatment of generalized anxiety disorder.

Source(s) of Funding: Eli Lilly and Company

POSTER NO. 22

MODAFINIL IMPROVES COCAINE ABSTINENCE IN COCAINE-DEPENDENCE: A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Objective/Background: Modafinil is a novel wake-promoting agent with low abuse potential. Its potential beneficial effects in patients with cocaine dependence are based on its ability to normalize cocaine-induced neuroadaptations, increase activity in the frontal cortex, and reverse cocaine withdrawal symptoms such as cognitive dysfunction and sleepiness. Results of preliminary open-label studies suggest that modafinil may facilitate cocaine abstinence and improve treatment retention in cocaine dependence. This is the first double-blind, placebo-controlled trial to evaluate modafinil for the treatment of patients with cocaine dependence.

Methods: This double-blind, placebo-controlled study included 62 cocaine-dependent outpatient subjects. None of the subjects were addicted to other substances or had unstable medical or psychiatric disorders. After signing informed consent, patients were randomized to receive modafinil 400 mg/day (n = 30) or matching placebo (n = 32) given as a single morning dose for 8 weeks. All patients received twice-weekly cognitive behavioral therapy (CBT). Cocaine use was assessed by urine testing three times weekly for benzoylecgonine (BE), a cocaine metabolite. Abstinence was defined as the number of BE negative urines supplied, divided by the total number of urines requested (ie, three per week).

Results: Forty-four (71%) of the subjects were male and 18 (29%) were female (mean age = 44.5 years [SD 8.7]). Modafinil-treated subjects had higher mean abstinence rates (42.4%) than placebo-treated subjects (21.6%). Longitudinal generalized estimating equation models showed a significant main effect for cocaine abstinence in the modafinil group compared with the placebo group (odds ratio = 2.78, p = 0.01). During the 8-week trial, modafinil was well tolerated. No serious adverse events occurred during the study and none of the 30 modafinil-treated subjects discontinued modafinil because of adverse effects.

Conclusion: These findings indicate that modafinil is effective for cocaine dependence. Further, larger controlled studies are warranted in this population.

Source(s) of Funding: NIDA (P50DA12756) and Cephalon, Inc.

POSTER NO. 23

RESPIRATORY AND AUTONOMIC PANIC DISORDER SUBTYPES: CLINICAL CORRELATES AND RESPONSE TO ALPRAZOLAM-XR

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Objective/Background: Research suggests that there may be at least 2 clinically relevant subtypes of panic disorder, a respiratory subtype and an autonomic subtype, each associated with different clinical characteristics.

Methods: Data were combined from 2 flexible-dose studies in which patients meeting DSM-III criteria for panic disorder were randomized, double-blind, to 6 weeks of treatment with either alprazolam-XR (ALP-XR; N=172; 59.9% female) or placebo (PBO; N=162; 59.3% female). A Sheehan Patient-Rated Anxiety Scale (SPRAS)-factor score > 8 was required to qualify a patient for either the respiratory or autonomic subtype (equivalent to moderate severity on 4 out of 5 symptoms). Response was defined as "much" or "very much" improved on the CGI-I.

Results: 213 patients (64%) had the respiratory subtype (26% with agoraphobia, baseline mean weekly spontaneous vs. situational attacks: 3.7 vs. 4.1); and 195 patients (58%) had the autonomic subtype (26% with agoraphobia, baseline mean weekly spontaneous vs. situational attacks: 3.8 vs. 4.5). For the respiratory subtype, treatment with ALP-XR resulted in significantly greater improvement than placebo in total panic frequency at LOCF endpoint (-5.1 + 0.66 vs. -2.4 + 0.65; $p < 0.01$), and significantly higher CGI-I responder rates at LOCF endpoint (74% vs. 45%; $p < 0.01$). For the autonomic subgroup, treatment with ALP-XR resulted in significantly greater improvement than placebo in total panic frequency at LOCF endpoint (-5.4 + 0.67 vs. -3.0 + 0.66; $p = 0.01$), and significantly higher CGI-I responder rates at LOCF endpoint (72% vs. 40%; $p < 0.01$). Additional data will be presented regarding these 2 panic subtypes, as well as the efficacy of ALP-XR in improving respiratory and autonomic symptomatology.

Conclusion: ALP-XR demonstrates significant efficacy in both the autonomic and respiratory subtypes of panic disorder.

Source(s) of Funding: Pfizer, Inc.

POSTER NO. 24

SUSTAINED REMISSION/EUTHYMIA WITH QUETIAPINE MONOTHERAPY FOR BIPOLAR MANIA

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Objective: Determine the effectiveness of quetiapine in the treatment of bipolar mania using different criteria for clinical remission/euthymia.

Methods: Three cut-off criteria for remission/euthymia were used to analyze 12-week, randomized, double-blind, monotherapy data obtained from patients hospitalized with bipolar I mania who received quetiapine (up to 800 mg/day) or placebo in two studies of the same design.

Results: Mean YMRS scores at entry were 33.3 (n=208) and 33.5 (n=195) in the quetiapine and placebo groups, respectively. After 3 weeks, remission/euthymia rates with quetiapine monotherapy versus placebo were: 37.5% vs 23.1% (YMRS 12); 35.6.2% vs 21.5% (YMRS 12 + MADRS 10); and 35.1% vs 20.0% (YMRS 12 + MADRS 8) ($P<0.01$). After 3 months, rates of remission/euthymia versus placebo were: 65.4% vs 35.9% (YMRS 12); 60.1% vs 30.8% (YMRS 12 + MADRS 10); and 58.7% vs 29.7% (YMRS 12 + MADRS 8) ($P<0.001$). The average daily dose of quetiapine in responders was 575 mg and 598 mg at each assessment, respectively.

Conclusions: Quetiapine at a target dose of approximately 600 mg/day leads to significant improvements in the proportion of patients with mania achieving clinical remission/euthymia, regardless of the assessment criteria used. Meaningful improvements with quetiapine monotherapy are sustained for at least 3 months.

Source(s) of funding: This research was supported by AstraZeneca.

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POSTER NO. 25

PARTIAL REPORTING OF THE CLINICAL GLOBAL IMPRESSION-IMPROVEMENT SCALE IN POSTTRAUMATIC STRESS DISORDER CLINICAL TRIALS: ARE PTSD CGI-IS MIA?

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V.A. San Diego Healthcare System

Background: Psychiatric rating scales are used to quantify outcomes of clinical trials, assessing data as specific as a symptom; as broadly as a syndrome or disorder; or even globally, such as quality of life or level of function.

Objective: This poster shall examine the manner in which the widely-used Clinical Global Impression-Improvement scale (CGI-I) is reported in Posttraumatic Stress Disorder (PTSD) clinical trials. This scale rates overall therapeutic effect (considering together positive and negative changes, such as medication efficacy and side effects) relative to the start of treatment. The CGI-I's anchor points are: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (unchanged), 5 (minimally worse), 6 (much worse), and 7 (very much worse).

Method: Articles which reported original medication trials for PTSD were identified by a PubMed computer-based literature search, using the medical subject heading "stress disorders, posttraumatic/drug therapy" for the period January 2000 through December 2003 in the *American Journal of Psychiatry, Journal of Clinical Psychiatry, Archives of General Psychiatry*, and the *Journal of the American Medical Association (JAMA)*. Nineteen articles were identified with PTSD and a specific medication in their titles.

Results: Of the 15 articles which used 1 or more rating scales for measuring outcome, 9 reported CGI-I scores of 1 and 2 (very much improved and much improved), as indicators of medication "response." One article (11% of the 9 articles reporting CGI-Is of 1 and 2) additionally designated CGI-I scores of "$\geq$ 3" as a criterion (with other obligatory criteria) for classifying "relapse." One article (11% of the 9 articles reporting CGI-Is of 1 and 2) also reported a specific CGI-I score from 3 to 7, thus documenting CGI-Is for every member of the intent-to-treat cohort.

Conclusion: The convention of selectively reporting CGI-Is of 1 and 2 ("responders"), and very rarely reporting CGI-Is of 3, 4, 5, 6 and 7 (non-"responders"), results in an incomplete and non-specific CGI-I representation of medication non-"responders" (with unreported CGI-Is) whose clinical outcomes may vary widely, from minimally improved (3), to unchanged (4), to minimally worse (5), to significantly worse (6, 7). Though drop-out rates and tolerability reports regarding frequency and severity of side effects are usually included in most trials, the absence of CGI-Is 3 through 7 (the non-"responders") reduces the focus on the clinical status of the **minimally improved** and the **unchanged** (with CGI-Is of 3 and 4) and the globally **worse** (with CGI-Is of 5, 6 and 7). Indeed, the missing-in-action cohort (with CGI-Is of 3 through 7) represents all of the study members with **unfavorable** outcomes due to lack of medication efficacy, or medication intolerability, prohibitive side effects, safety concerns, adherence issues, clinical deterioration, acute exacerbation, or relapse.

This group of non-"responders" (with CGI-Is of 3-7), all members of the intent-to-treat cohort, should not be absented from clinical trial reports. Indeed, knowledge of less-than-ideal outcomes would be much appreciated by prescribing practitioners who have the responsibility (the "**prescriber's burden**") for mitigating, by dosage adjustment or medication change, the absence of positive effects or the presence of negative effects of the pharmaceuticals they order.

Source of Funding: VA San Diego Healthcare System

POSTER NO. 26

ARIPRAZOLE AS AN AUGMENTOR OF SSRIs IN MOOD AND ANXIETY DISORDER PATIENTS

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Introduction: Recent studies have shown that almost one-third of patients treated with an antidepressant, at an adequate dose and duration, are non-responders. Many psychotropic agents have been used in recent years to treat these patients who are either unable to tolerate or not able to achieve remission following an adequate trial of their antidepressant and/or anxiolytic medications.

Method: We report 19 cases of augmentation with Aripiprazole in patients with mood and anxiety disorders, who were not full responders to a variety of SSRIs. Patients had been on a stable dose of their concomitant medications for at least 1 month prior to initiation of treatment with aripiprazole. Patients were prescribed aripiprazole tablets at the initial dose of 15 mg q.d. with the possibility of increasing or decreasing the dose as clinically indicated. The primary outcome measure was the Clinical Global Impression of Improvement. To our knowledge these are the first reported findings in this type of patient population.

Results: Nineteen subjects took at least one dose of aripiprazole and returned to complete the follow-up assessments. Seven subjects discontinued the drug prematurely. The mean aripiprazole dose in our patients was 17 mg/day. The mean interval between baseline visit and follow-up visit was 5.2 ± 2.2 weeks. In the intent-to-treat analysis, the mean CGI-S at baseline was 5.4 and CGI-S at endpoint was 3.9. This difference was statistically significant with a p-value of .0002. Response was defined as patients with CGI-Improvement score of 'very much improved' or 'much improved'. In the intent-to-treat analysis 53% of patients (10/19) showed a full-response. In the completer analysis 67% of patients (8/12) showed a full response.

Discussion: The patients entered into this study were all treatment refractory or intolerant to standard doses of antidepressants and/or anxiolytics. 74% of patients had previously failed trials of atypical antipsychotics either due to lack of response or lack of tolerability. In this severely treatment refractory group, the rate of full-response to augmentation with aripiprazole was impressive and encouraging. One of the main limitations of our study is the retrospective measurements. An open-label protocol with a design similar to this present study is currently enrolling patients at our research center, using prospective measurements.

Conclusion: Our pilot open trial suggests that aripiprazole treatment may be efficacious among mood and anxiety disorders with refractory illness. Further double-blind, placebo controlled trials are needed and are in the preliminary stages at our research center.

Disclosure: This work was funded by the Mood and Anxiety Disorder Institute of the Massachusetts General Hospital.

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POSTER NO. 27

RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND TRIAL OF PAROXETINE CONTROLLED RELEASE IN IRRITABLE BOWEL SYNDROME

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Objective: Open label studies have suggested a possible therapeutic role for selective serotonin uptake inhibitors (SSRI) in IBS. In the first, double-blind, placebo-controlled study of SSRI in IBS, we examined the efficacy and safety of paroxetine controlled release (CR) in the treatment of IBS.

Methods: Enrollment of 72 subjects has been completed in an ongoing, double-blind, parallel group, prospective study followed by an open-label extension phase. Data presented here include 57 subjects with a diagnosis of IBS who were randomized to receive paroxetine CR (dose 12.5-50 mg per day) or placebo for 12 weeks. Efficacy was measured by a two point or greater reduction in Clinical Global Impression- improvement (CGI-I) scores and a one-point or greater reduction for Clinical Global Impression- Severity (CGI-S) scores from baseline to end of treatment (LOCF). Two tailed t tests, chi square and ANOVA were used to compute between group differences and effect sizes.

Results: The mean age of the sample was 49 years, 73% were women, and 77% were Caucasian. Ten (17.5%) subjects dropped out of the study. The dropout rate was similar in the drug and placebo groups. Analysis on 47 completed patients showed that 16 (73%) of subjects in the drug group showed a 2 point or greater improvement in CGI-I scores compared to 7 (27%) in the placebo group (Fisher's Exact; p=0.000). 15 out of 22 (68%) subjects receiving paroxetine CR had one point or greater reduction in CGI-S scores compared to 6 out of 25 (24%) receiving placebo (Fisher's Exact; p=0.003). IBS patients with primary complaint of diarrhea, constipation or both were equally likely to respond to paroxetine CR. The mean paroxetine CR dose was 33 mg per day. There were no significant differences in the prevalence of sexual side effects (drug ==22%, placebo=12%), sedation (drug=9%, placebo=16%), dry mouth (drug=26%, placebo=12%), nausea (drug=17%, placebo=24%) between the two groups.

Conclusions: Paroxetine CR appears to be well-tolerated and superior to placebo in the treatment of IBS using clinical global impression measures. Further analysis of the data that includes self-reported efficacy measures on interactive voice response system (IVRS) will be performed to clarify the overall efficacy of paroxetine CR. However, it seems that SSRIs may have a therapeutic role in reducing symptoms of IBS in clinical populations.

Funding: GlaxoSmithKline

POSTER NO. 28

ATYPICAL ANTIPSYCHOTICS IN THE TREATMENT OF MANIA: A META-ANALYSIS OF RANDOMIZED CONTROLLED MONOTHERAPY TRIALS

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Introduction: Controlled trials have demonstrated efficacy for atypical antipsychotics in the treatment of mania in bipolar disorder. However, there are no published comparisons of individual atypical antipsychotics. Therefore, we conducted a systematic review and meta-analysis of randomized, placebo-controlled monotherapy trials of atypical antipsychotics.

Methods: We included primary studies that prospectively compared one of the atypical antipsychotics approved for any indication by the U.S. Food and Drug Administration as of January 2004 (aripiprazole, clozapine, quetiapine, risperidone, ziprasidone, olanzapine) with a placebo control group in bipolar mania. Studies were identified using Medline search, reviews of meeting proceedings, as well as consultation with study investigators. We attempted to include all studies where results have been analyzed and presented in any forum; thus, there was no requirement that papers be published in a peer-reviewed journal for inclusion. Analyses were performed on the change in Young Mania Rating Scale or Mania Rating Scale total score from baseline to endpoint, using last observation carried forward and computing the difference in change scores between each drug and its corresponding placebo arm. A random-effects model with fixed drug effects was used to combine the studies and make comparisons of the drugs to each other and to placebo.

Results: Data from 12 placebo-controlled monotherapy trials involving a total of 3593 subjects (including 1709 placebo-treated subjects) with bipolar mania (pure and/or mixed states) were obtained. All studies reported day 21 endpoints, except for two trials of olanzapine (day 28 and 42) and one of risperidone (day 28). Three of these trials included an active comparator in addition to the placebo arm. No trials were identified that included clozapine. All of the other drugs demonstrated significant efficacy (i.e., all confidence intervals exclude zero). However, after adjusting for multiple comparisons, pairwise comparisons of individual effects identified no significant differences between drugs.

Conclusion: The five newer atypical antipsychotics are all superior to placebo in the treatment of bipolar mania. Cross-trial comparisons further suggest that differences in efficacy between the drugs, if any, are likely to be small.

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POSTER NO. 29

ZIPRASIDONE FOR TREATMENT-REFRACTORY GENERALIZED ANXIETY DISORDER: AN OPEN-LABEL, FLEXIBLE-DOSE PILOT STUDY

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Objective/Background: To provide pilot data on the efficacy and safety of ziprasidone for the treatment of generalized anxiety disorder (GAD) in adults who have failed a trial of at least one first line agent. Despite the high rate of response of GAD to acute benzodiazepine therapy, no more than 40% reach symptomatic remission. Similarly low remission rates below 40% are observed for venlafaxine XR and for paroxetine. Ziprasidone is a potent 5HT1A agonist , and has a greater affinity for cloned human 5HT1A than does risperidone, olanzapine, quetiapine or clozapine. Ziprasidone's serotonergic properties may make it a useful agent in the treatment of generalized anxiety disorder.

Methods: 10 outpatients with a principal diagnosis of generalized anxiety disorder who had not responded sufficiently (defined by a HAM-A score of 16 or greater) after 8 weeks of treatment with first line anti-anxiety agents such as sertraline, paroxetine, venlafaxine, buspirone or 4 weeks on an adequate dose of benzodiazepine were recruited for the study. Patients received ziprasidone, at doses between 20 to 80 mg daily as tolerated in divided doses, as a single agent or in addition to their current treatment for 7 weeks, followed by a 3-7 day taper. Patients were assessed at weekly intervals using the HAM-A as a primary outcome measure, and the CGI-S as a secondary outcome measure.

Results: Patients had a mean age of 53.3 +/- 8.5 years at baseline; 50% were male. Two patients received concomitant benzodiazepine during the course of the study; all others received no comcomitant psychotropics. Patients had failed a mean of 2.3 +/-1.8 trials of first line medications for GAD before entering the study. Mean HAM-A at baseline was 19.8 +/- 3.2, while mean CGI-S was 4.1 +/- 0.32 at baseline. Adjusted mean scores at week 7 (LOCF analysis) were 8.7 +/- 4.3 for HAM-A, and 2.5 +/- 1 for CGI-S. Mean HAM-A at week 1 (with 100% of patients receiving 20 mg ziprasidone daily) was 13 +/- 6.

Conclusion: Ziprasidone, at doses as low as 20 mg daily shows promise as an anxiolytic in patients with GAD who have failed first line agents. In some patients, clinically significant improvement was seen as early as week 1. As a group, mean HAM-A scores dropped by over 6 points by week 1. A double-blind, randomized controlled clinical trial is needed to demonstrate ziprasidone's future role in the treatment of treatment-resistant GAD.

Source(s) of Funding: Research was supported by an investigator initiated grant from Pfizer pharmaceuticals.

POSTER NO. 30

ADD-ON AND MONOTHERAPY TOPIRAMATE IN CIVILIANS WITH CHRONIC NON-HALLUCINATORY POSTTRAUMATIC STRESS DISORDER: A PROSPECTIVE OPEN-LABEL STUDY

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Objective/Background: To see if therapeutic effects of topiramate on PTSD observed in a prior study were confirmable in a new sample, a prospective, open study was done to examine acute response in chronic, non-hallucinatory civilian PTSD.

Methods: Thirty-three never-previously-reported, consecutive civilian adult outpatients (mean age 46 years, 85% female) with DSM-IV chronic PTSD, excluding those with concurrent auditory or visual hallucinations, received topiramate either as monotherapy (n=5) or augmentation (n=28). The primary measure was change in the PTSD Checklist-Civilian Version (PCL-C) at baseline and at 4 weeks, with response defined as a =30% reduction in PTSD symptoms.

Results: For those taking the PCL-C at both baseline and week 4 (n=30), total symptoms declined by 50% at week 4 (paired t-test, df=29, P<.001) with similar subscale reductions for reexperiencing, avoidance/numbing, and hyperarousal symptoms. The response rate at week 4 was 77%. Age, sex, bipolar comorbidity, age of onset, duration of symptoms, severity of baseline PCL-C score, and monotherapy vs. add-on medication administration did not predict reduction in PCL-C scores. Median time to full response was 9 days and median dosage 50 mg/d.

Conclusion: Positive open-label findings in a new sample converge with findings of a previous study. The use of topiramate for treatment of chronic PTSD, at least in civilians, warrants controlled clinical trials.

Source(s) of Funding: Ortho-McNeil Pharmaceutical, for poster presentation and meeting support.

POSTER NO. 31

TIAGABINE IMPROVES SYMPTOMS OF SOCIAL ANXIETY DISORDER: AN OPEN- LABEL STUDY

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Objective/Background: Gamma-amino-butyric acid (GABA) has been implicated in the pathophysiology of certain anxiety disorders. Tiagabine, a selective GABA reuptake inhibitor (SGRI) at the GAT-1 transporter, increases the availability of synaptic GABA. Tiagabine been shown to reduce symptoms of anxiety in open-label studies. The effectiveness and tolerability of tiagabine in patients with social anxiety disorder (SAD) were evaluated.

Methods: Adults (=18 years of age) fulfilling DSM-IV criteria for SAD were enrolled in this 12-week, open-label study. Tiagabine was initiated at 4 mg/d (2 mg bid with food) and then individually titrated weekly by 4 mg (2 mg bid) increments up to a maximum dose of 16mg/d (8 mg bid). Primary efficacy assessments were the changes from baseline to last visit in the Liebowitz Social Anxiety Scale (LSAS) and Clinical Global Impression of Change Scale (CGI-C). Secondary efficacy assessments included the Hamilton Anxiety Rating Scale (HAM-A), Social Phobia Inventory (SPIN), Sheehan Disability Scale (SDS), and Pittsburgh Sleep Quality Index (PSQI).

Results: Of 63 patients enrolled in this ongoing study, 57 were treated with tiagabine, 51 were included in the last-observation-carried-forward (LOCF) efficacy analyses, 26 (40%) have completed 12 weeks of tiagabine treatment, and 9 (14%) withdrew due to adverse events. Mean duration of SAD was 6.0 years (range 0-47 years). Mean final tiagabine dose was 9.8 mg/d (range 4-16 mg/d). Tiagabine improved symptoms of SAD, as demonstrated by significant reductions in all measures of anxiety and sleep . Likewise, overall clinical condition was significantly improved ($P<0.001$); 43.8% of patients were responders on the CGI-C ("much improved" or "very much improved"). HAM-A scores showed that 53.5% of patients were remitters (total HAM-A =7). Of the 26 patients completing 12 weeks of tiagabine treatment to date, 62.5% were CGI-C responders and 69.2% were remitters (total HAM-A =7). Most commonly reported adverse events were somnolence (n=18), dizziness (n=14), nausea (n=10), and headache (n=10).

Conclusion: The findings from this open-label study suggest that Tiagabine may be a treatment option for SAD. Tiagabine was generally well tolerated. Further controlled studies are warranted to fully elucidate the efficacy of tiagabine in SAD.

Source(s) of Funding: This study was supported by Cephalon, Inc., West Chester, PA.

POSTER NO. 32

METHODOLOGICAL CONSIDERATIONS IN A GAD TREATMENT TRIAL

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Objective/Background: Traditional registration clinical trials frequently incorporate approaches, such as a placebo run-in period, designed to boost the effect size. We investigated the potential effect of a placebo run-in design element on clinical trial results in subjects with DSM-IV generalized anxiety disorder (GAD).

Methods: Data from a multicenter, 10-week, placebo-controlled, flexible dosing trial of sertraline (50-200mg/d) in GAD subjects that did not utilize placebo run-in period, were used. To approximate a placebo run-in, a data subset comprising subjects who experienced < 20% decline in HAM-A total scores during study week 1 (at half minimal dose) was created. Results for full ITT data set (n=326) were compared with the subset to evaluate the impact of elimination of hypothesized placebo responders on treatment effect sizes and statistical significance.

Results: The placebo run-in approximation demonstrated a larger effect size and smaller p-values on all main outcome variables and lower placebo response rate compared with the full sample despite a 42% reduction in sample size (n=190).

Conclusion: Results indicate a potential for an artificially enhanced treatment effect with a placebo-run in period. These results have implications for generalizability to a general clinical population from standard, placebo run-in design utilized in corporate-sponsored, registration trials.

Source(s) of Funding: Unrestricted Investigator Initiated Grant to Dr. Brawman-Mintzer from Pfizer Pharmaceutical Co.

POSTER NO. 33

FACTORS ASSOCIATED WITH MISSED FIRST APPOINTMENTS IN SUBJECTS VOLUNTEERING TO PARTICIPATE IN A CLINICAL TRIAL OF POSTTRAUMATIC STRESS DISORDER

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Objective: This study aimed to ascertain the no-show rate among subjects who volunteered to participate in a PTSD clinical trial. It also sought to identify factors associated with missed first appointments in the research clinic.

Methods: A retrospective review of 130 telephone intake screens of subjects' who contacted the clinic to volunteer their participation in the PTSD clinical trial was conducted. Nine variables potentially associated with missed first appointments were assessed. Also reviewed were number of symptoms subjects reported in the 3 symptom categories of PTSD; re-experiencing the trauma, avoidance of trauma related situations, and hyperarousal. Sixty subjects who missed their first appointments were surveyed and asked to rate their level of satisfaction on a 5-point Likert scale with regard to their first contact with the clinic and also indicate their main reason/s for having missed their appointment.

Results: The no-show rate among the research subjects was 53.84 % (70/130), while among the non-research patients in the general clinic was 16.97% (425/2505). Use of the stepwise discriminant function analysis identified age, type of trauma and number of avoidance symptoms that significantly separated volunteers who showed up for the research appointments from those who did not. {Wilks' Lambda: 0.688, F (3, 85) =12.85), P < 0.001}. A detailed examination of the type of trauma on 'no-show' rates using a 2 groups by 4 category of trauma table was analyzed by Pearson chi square which confirmed the difference between the groups. X2 = 12.54, df = 3, p= 0.0057. Younger subjects, those with a non-sexual history of trauma and those reporting a lower number of avoidance symptoms during the initial telephonic interview were more likely to miss their appointments. A descriptive analysis of the survey data showed that the respondents were overall satisfied with their initial contact with the clinic. Reasons indicated by the respondents for missing their appointments included child care problems, work absenteeism, transportation and concerns about participating in a trial. They indicated that a reminder phone call, more study information and increased payment for participation may help to increase study participation.

Conclusions: The results suggest a higher no-show rate for patients in a research clinic compared to the general psychiatric clinic. Younger age, non-sexual trauma and fewer avoidance symptoms were associated with missed first appointments. Addressing issues like child care, transportation, reminder phone calls and increased payment may improve patient recruitment. Since patients with greater symptoms are more likely to keep their first appointments, it dispels the perceived notion that patients in clinical trials are not as sick as the 'real world' patients.

Disclosure/Source of funding: Supported in part by Ortho McNeil Pharmaceuticals

POSTER NO. 34

ESCITALOPRAM IN THE TREATMENT OF MAJOR DEPRESSION WITH COMORBID GAD

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Objective/Background: Current evidence exists demonstrating that escitalopram is effective in treating Major Depression. There is accumulating evidence suggesting the efficacy of escitalopram in anxiety disorders. However there is a lack of evidence of the efficacy of escitalopram in subjects presenting with both symptoms of comorbid Major Depression with Generalized Anxiety Disorder. This is important as subjects often present with both symptoms in clinical practice.

Methods: This is a twelve week open label trial evaluating escialopram upto 20 mg/day in subjects diagnosed with Major Depression and comorbid Generalized Anxiety Disorder. Subjects needed a minimal score of 18 on the HAMA and HAMD to be accepted in the study. Subjects were seen weekly for the first five weeks followed by biweekly visits. Primary efficacy assessments include HAMA, HAMD, Clinical Global Impression Severity (CGI-S) and Clinical Global Impression of Change (CGI-C). Response was defined as a CGI-S of 1 or 2.

Results: Seventeen subjects entered the study. The mean HAMA score at baseline was 26.8 and and HAMD score was 23.6. Scores reduced to HAMA=10 HAMD=8 (LOCF).Fifteen subjects were evaluable, i.e. had at least three weeks of treatment. Of the fifteen subjects 11 were considered as responders with a CGI of 1 "normal" or 2 "minimal symptoms" at the end of treatment. Four subjects were considered as non-responders to treatment. Bothsymptoms of depression and anxiety improved. Side effects included drowsiness were tolerable.

Conclusion: Escitalopram was well tolerated. Escitalopram was effective in treating subjects with anxiety and comorbid depression. Double-blind studies are warranted

Source(s) of Funding: Forest Laboratories Harborside Financial Center, Plaza V, Jersey City, NJ

POSTER NO. 35

QUETIAPINE REDUCES PERSISTENT ANXIETY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Objective/Background: Many patients with Major Depressive Disorder (MDD) present with concomitant symptoms of anxiety, agitation, and sleep disturbance. The initial anxiolytic effects of antidepressants may be short-lived such that the depression improves but anxiety symptoms persist. The anxious symptoms may be related to an incompletely treated anxious-depressed state and/or a residual side effect of an SSRI medication. This open-label study evaluated the anxiolytic efficacy and safety of quetiapine in treated MDD patients on stable doses of SSRI's who presented with persistent anxiety.

Methods: Three sites participated in a 4-week open-label trial of quetiapine added to existing SSRI's. Eligible, consenting subjects (ages 18 to 60) met DSM-IV criteria for MDD, were taking stable doses of an SSRI (or venlafaxine) for at least 6 weeks prior to baseline, had a HAM-A score > 20 and a HAM-D score < 17 at screening and baseline. Ratings included the Hamilton Anxiety scale (HAM-A), Hamilton Depression scale (HAM-D), Zung Anxiety scale, CGI-S and CGI-I, Pittsburgh Sleep Quality Index (PSQI), Barnes akathisia scale (BAS) and Simpson-Angus scale (SAS). Quetiapine was started at 25 mg po AM on day 1, increased to 25 mg po B.I.D. on day 2, and titrated afterwards based upon clinical response. The antidepressant dose remained unchanged.

Results: 21 subjects met inclusion/exclusion criteria and were started on study medication. Their antidepressants included sertraline (3), fluoxetine (3), citalopram (6), paroxetine (4), and venlafaxine (6). Stable quetiapine doses were achieved between weeks 1 and 2. The mean quetiapine dose was 105 ± 65.6 (SD) mg/day with a range from 25-300 mg/day. The mean Ham-A score improved significantly from 25.1 ± 5.5 (SD) at baseline to 8.3 ± 5.9 at endpoint ($p < 0.001$). Similarly, there was significant improvement on the Zung scale ($p < 0.001$), CGI-S ($p < 0.001$), and PSQI ($p < 0.001$). The Ham-D improved from 14.6 ± 2.4 (SD) at baseline to 7.6 ± 5.1 at endpoint ($p < 0.001$) with changes noted primarily in the anxiety, somatic, and sleep items. Ten subjects described sedative-like effects that were mostly transient within the first week of treatment. 5 subjects were withdrawn from the study within the first week. However, 15 of the remaining 16 subjects (94%) had Ham-A scores drop > 50% from baseline. No EPS were noted on either the BAS or SAS.

Conclusion: In this open-label study, supplemental quetiapine significantly reduced persistent anxiety in treated depressed patients who had been taking stable doses of SSRI's or venlafaxine. These results need to be interpreted with caution given the open-label nature of the study.

Source(s) of Funding: AstraZeneca Pharmaceuticals LP (Wilmington, Delaware)

POSTER NO. 36

REAL-TIME IDENTIFICATION OF MISSING DATA IN A FORMS-BASED PROTOCOL MANAGEMENT SYSTEM

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Objective/Background: Case report forms are typically used to gather and organize clinical research data. While it is possible to require completion of all fields on any form, missing data will inevitably occur in the course of data collection. Rapid identification of missing data is one of the first steps that may lead to reduction of missing data and more informative studies.

Methods: We used Open Infrastructure for Outcomes (OIO), a free/open-source web-based clinical and research data management software, as the starting point in designing a generator of real-time missing data reports. The OIO software uses web-forms to model case report forms. A clinical research protocol consists of a collection of case report forms and a set of workflows that describe the flow of research subjects through the protocol (http://www.TxOutcome.Org). An existing reports module in OIO extracts, transforms, and loads data from multiple forms into data mining tables (ETL procedure) for drill-down query and statistical analysis. For the purpose of real-time missing data reporting, this ETL procedure is too cumbersome and slow.

Results: To support flexible real-time reporting, we designed and added a new "Live Reports" module that allows the construction of real-time reports through any web-browser. Study monitors and/or investigators can select individual fields from any clinical report form to include on the "Live Report". All missing data are noted in red and their source forms are available for review and modification through a single click. After the source forms are changed, the live report can be regenerated through a single click to display the up-to-date status of the remaining missing data, if any.

Conclusion: Real-time reports of missing data are useful for timely identification and reduction of missing data in clinical trials. For forms-based research information systems, it is possible for non-programmer end-users with minimal training to rapidly construct real-time reports to display missing data instances. Furthermore, providing single mouse-click access to the source form facilitates the reduction of missing data.

Source(s) of Funding: None

POSTER NO. 37

ABRUPT DISCONTINUATION OF ALPRAZOLAM IN PANIC PATIENTS: ANXIETY DURING THE NEXT 24 HOURS

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Objective/Background: Alprazolam is well established as a safe and effective treatment for panic disorder with or without agoraphobia. However, inter-dose symptom breakthrough and difficulty discontinuing chronic treatment have been reported, although data about the factors involved are limited. This study proposed to quantify the effects of declining drug plasma levels and an anxiety-prone cognitive style on emerging anxiety in panic disorder patients within 24 hours after abrupt discontinuation of chronic alprazolam treatment.

Methods: Twenty eight patients meeting DSM-III-R criteria for panic disorder with or without agoraphobia were treated for nine weeks with a fixed dose of alprazolam 1 mg. q.i.d. They were admitted to the Clinical Research Center (CRC) for 24 hours, beginning at 9 PM, after week 8 and again after week 9 of treatment. On one occasion, treatment was maintained; on the other, placebo was substituted for alprazolam doses scheduled for 6 AM, 11 AM, and 4 PM. Medication was double-blind. The order of the two sessions was random. Anxiety was measured with the Profile of Mood States (POMS) and blood samples were drawn before dosing on admission and seven times next day between 6 AM and 9 PM. Blood samples were separated, frozen, and assayed for plasma alprazolam using capillary gas chromatography/negative ion chemical ionization mass spectrometry. The Anxious Thoughts and Tendencies questionnaire (AT&T), a putative measure of an anxiety-prone cognitive style, was administered before the first admission to the CRC. Preliminary analyses eliminated some variables as unimportant, e.g., order. A random regression procedure (SAS MIXED) was used to analyze the data from the seven repeated trials on each day after admission, with Ln(POMS Anxiety + 1) as the dependent variable and AT&T score, baseline POMS Anxiety (on admission), Ln(plasma alprazolam), and trial as independent variables. Plasma level and trial were entered as random variables, assuming unstructured covariance.

Results: The table (column 5) shows that each variable made a significant independent contribution to the level of anxiety after medication discontinuation. The last three columns of the table indicate the magnitudes of these effects on the POMS Anxiety score in its original metric (scaled 0-4). Anxiety increased by 0.71 units over the range of AT&T scores (1.07-3.60) observed in this study (row 1), even with control for the initial level of anxiety (row 2), which increased anxiety by 0.84 units over the observed range of logged baseline anxiety (0-1.61). As logged alprazolam level dropped from 5.41 to 2.13, anxiety increased by 1.09 units, the largest single effect. In addition, anxiety increased slightly across trials, perhaps because of building negative anticipation, fatigue from the procedures, or diurnal variation.

Conclusion: The results suggest that the AT&T measures an anxiety-prone cognitive style that is at least partly independent of state anxiety. This factor may have obscured clinical/plasma level correlations in studies that classically did not take account of cognitions. It also may help to explain the demonstrated effectiveness of cognitive therapy in alleviating the experience of withdrawal symptoms.

Source(s) of Funding: The Upjohn Company; The University of Chicago; The University of New Mexico; NIMH General Clinical Research Centers.

POSTER NO. 38

A DOUBLE-BLIND COMPARISON OF VENLAFAXINE XR, SERTRALINE, AND PLACEBO IN THE TREATMENT OF PTSD

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Objective/Background: This double-blind, randomized, placebo-controlled, 3-month clinical trial was conducted to compare the efficacy of venlafaxine extended release (XR) and sertraline in reducing the symptoms of moderate to marked posttraumatic stress disorder (PTSD).

Methods: In this double-blind, parallel-group study, 537 adult outpatients were randomly assigned to receive a flexible dose of venlafaxine XR (37.5-300 mg/day), a flexible dose of sertraline (25-200 mg/day), or placebo for 12 weeks. After day 5, the minimum daily doses of venlafaxine XR and sertraline were 75 mg and 50 mg, respectively. Patients were included if they had a primary diagnosis of DSM-IV PTSD, PTSD symptoms for $\geq$6 months, and a 17-item Clinician-Administered PTSD scale (CAPS-SX_{17}) score $\geq$60. The primary efficacy measure was the change from baseline to endpoint (week 12 or time of discontinuation) in the CAPS-SX_{17} score. Secondary assessments included the frequency of remission (CAPS-$SX_{17} \leq 20$), time to remission, PTSD symptom-free days (based on CAPS-SX_{17} scores), and changes from baseline to endpoint in the following: the CAPS- SX_{17} symptom cluster scores for avoidance/numbing, arousal, and re-experiencing/intrusion; the Connor-Davidson Resilience Scale; Clinical Global Impression-Severity of Illness Scale; Global Assessment of Functioning scale; Davidson Trauma Scale (DTS); 17-item Hamilton Depression Rating Scale; Numbing, Intrusion, and Hyperarousal scale; Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF); Sheehan Disability Scale (SDS); Stress Vulnerability Scale (SVS); Work Questionnaire; and Utilization and Cost Questionnaire.

Results: Mean maximum daily doses were 225 mg venlafaxine XR and 151 mg sertraline. Mean baseline-to-endpoint changes in CAPS-SX_{17} scores were -41.8, -39.4, and -33.9 for the venlafaxine XR ($P<0.05$ vs placebo), sertraline, and placebo groups, respectively. Mean baseline-to-endpoint changes for venlafaxine XR, sertraline, and placebo in CAPS-SX_{17} cluster scores were -13.0, -11.7, and -11.0 for Cluster B (re-experiencing); -17.1, -16.8, and -13.7 ($P<0.05$ both active treatments vs placebo) for Cluster C (avoidance/numbing); and -11.8, -10.9, and -9.2 ($P<0.05$ venlafaxine vs placebo) for Cluster D (hyperarousal). The venlafaxine XR group also showed significant improvement compared with the placebo group at week 12 for symptom-free days, DTS total score, Q-LES-Q total score, SVS total score, and the social life domain of the SDS ($P<0.05$). Remission rates were 30.2%, 24.3%, and 19.6% with venlafaxine XR ($P<0.05$ vs placebo), sertraline, and placebo treatments, respectively. Both treatments were generally well tolerated.

Conclusion: Venlafaxine XR is effective in the short-term treatment of patients with PTSD.

Source(s) of Funding: Wyeth Research

POSTER NO. 39

ARE ANXIETY DISORDERS UNDERDIAGNOSED AND UNDERTREATED IN ROUTINE PSYCHIATRIC PRACTICE?

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Objective/Background: 1) To assess rates of detection and diagnosis of anxiety disorders in routine psychiatric practice; 2) To examine patterns of treatment of patients with anxiety symptoms or diagnoses.

Methods: 615 psychiatrists from a full range of clinical settings participated in the American Psychiatric Practice Research Network's 1999 Study of Psychiatric Patients and Treatments (SPPT) generating nationally representative clinical data on 1,843 patients. Comparisons were also made with household respondents in the National Comorbidity Survey (NCS) who reported using specialty mental health services.

Results: The prevalence of anxiety disorders reported by psychiatrists in routine practice was much lower than the prevalence found in self-reported specialty mental health service users ascertained through a structured household interview. Phobias were 22 times more likely to be diagnosed in the NCS sample compared to the SPPT sample. PTSD was diagnosed at 5 times the SPPT rate, GAD at over 3 times the rate, and panic disorder at more than twice the rate. When SPPT patients with a DSM-IV anxiety disorder were combined with patients who had no reported anxiety disorder but with moderate or severe anxiety symptoms, the percentage in the SPPT sample increased 54.7%, closer to the level of anxiety diagnoses in the NCS sample (68.1%). Over 10% of SPPT patients with panic disorder were receiving neither psychotherapy nor anti-anxiety medication, while 14% of patients with no anxiety diagnosis, but moderate to severe anxiety symptoms were not receiving psychotherapy or anti-anxiety medication. Over 75% of patients with generalized anxiety disorder or panic disorder were receiving anti-anxiety medications, while less than two-thirds of patients with a phobia diagnosis were receiving these medications. The most commonly prescribed anti-anxiety medications included Alprazolam (16.7% of patients with anxiety disorders), Clonazepam (16.4%), and Paroxetine (15.9%).

Conclusion: These findings suggest that anxiety disorders are underdiagnosed and sometimes undertreated in routine psychiatric practice. Further research is needed to examine associated factors or clinical rationale for the findings such as clinical significance, comorbidity, and prevailing standards of diagnostic assessment. Longitudinal research that includes an in depth assessment of treatment patterns, sequencing, and outcomes is needed to assess the extent to which not diagnosing and treating anxiety disorders and symptoms results in poorer outcomes.

Source(s) of Funding: Development and support of the PRN has been funded by the American Psychiatric Foundation, the John D. and Catherine T. MacArthur Foundation, the Center for Mental Health Services and the Center for Substance Abuse Treatment.

POSTER NO. 40

IMPROVEMENT IN PATIENT-REPORTED FUNCTIONING IN PATIENTS WITH SOCIAL ANXIETY DISORDER TREATED WITH VENLAFAXINE XR, PAROXETINE, OR PLACEBO

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Objective/Background: Social anxiety disorder (SAD) is associated with substantial impairment in social and work function. We evaluated patient-reported functioning in SAD, comparing improvement with venlafaxine extended release (XR), paroxetine, and placebo.

Methods: Data were pooled from 5 multicenter, randomized, double-blind, placebo-controlled studies (2 of which were also paroxetine-controlled) of flexible-dose venlafaxine XR in patients with DSM-IV social anxiety disorder (overall N=1,736). Four studies were of 12-week duration and one was of 28-week duration; data were truncated at 12 weeks on the latter for consistency. Functional impairment was measured in terms of the social life and leisure activities, work, and family life and home responsibilities subscales of the patient-reported Sheehan Disability Scale (SDS). Baseline functional impairment and treatment-related improvement at the last observation on therapy over 12 weeks and adjusted for baseline score and treatment center was evaluated using analysis of covariance. The percentage of patients who achieved levels of very mild impairment ($\leq$1) was also compared across treatment groups, using the chi-square test of proportions.

Results: Overall at baseline, 69% of patients were "markedly" or "very severely" impaired in terms of the social activities subscale, 40% in terms of the work subscale, and 20% in terms of the family life subscale. Venlafaxine XR was associated with significantly greater improvement, relative to placebo, on all 3 subscales ($P<0.0001$). Further, a higher proportion of patients in the venlafaxine XR group achieved levels of very mild impairment on the work (venlafaxine XR 35.3% vs placebo 19.9%, $P<0.0001$), social life (venlafaxine XR 19.0% vs placebo 8.3%, $P<0.0001$), and family life (venlafaxine XR 48.2% vs placebo 36.4%, $P<0.0001$) subscales. Similar differences were also observed in all paroxetine vs placebo comparisons.

Conclusion: The International Consensus Group on Depression and Anxiety has recommended that patient-reported disability should be assessed in clinical studies of SAD. In these pooled clinical studies, patients were substantially impaired in social, work, and family-related functioning at baseline. Both venlafaxine XR and paroxetine were associated with significant improvement on all 3 components by end of treatment.

Source(s) of Funding: Wyeth Research

POSTER NO. 41

EFFICACY OF PREGABALIN IN CLINICALLY RELEVANT SUBTYPES OF GAD

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Objective/Background: To evaluate the efficacy of pregabalin, an alpha2-delta ligand, in clinically relevant subtypes of generalized anxiety disorder (GAD).

Methods: Data were collected from placebo-controlled Phase 2 and 3 studies of pregabalin as treatment of DSM-IV GAD. All pregabalin dosage groups (200 to 600 mg/day) were combined to yield the analysis sample, N=1282; female=60%; mean age=39.4 yrs; base HAM-A=25.4. Subgroups analyzed included those defined by the following variables: gender, age, severity (HAM-A of at least 26), subsyndromic depression (HAM-D of at least 15), severe somatic symptoms (HAM-A somatic factor of at least 12), and severe insomnia. A Week 4/6 LOCF-endpoint analysis was performed with responders defined as those having at least 50% reduction in HAM-A total score.

Results: Responder rates were significantly higher for pregabalin than placebo among males (56% versus 39%; $p<0.001$), females (51% versus 32%; $p<0.001$), and the elderly (55% versus 27%; $p<0.02$) and among patients with severe anxiety (61% versus 39%; $p<0.001$), subsyndromic depression (49% versus 31%; $p<0.001$), severe somatic symptoms (57% versus 35%; $p<0.0001$), or severe insomnia (60% versus 37%; $p<0.001$). Significantly greater improvement was observed in symptom factors used to define high-severity subgroups, including HAM-A somatic factor (Week 4/6 LOCF-endpoint change score, -7.3 +/- 0.3 versus 5.3 +/- 0.3; $p<0.0001$).

Conclusion: Pregabalin has broad-spectrum efficacy across clinically relevant subgroups in GAD.

Source(s) of Funding: Study funded by Pfizer.

POSTER NO. 42

PREDICTORS OF RESPONSE TO A PLACEBO-CONTROLLED, DOUBLE-BLIND TRIAL OF PAROXETINE CONTROLLED RELEASE IN FIBROMYALGIA

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Objective: A significant proportion of fibromyalgia patients fail to respond to pharmacological interventions. We determined whether certain clinical, behavioral and demographic variables at baseline predicted treatment response in fibromyalgia patients participating in an ongoing, 12-week, placebo-controlled, double-blind trial of paroxetine controlled release (CR).

Methods: One hundred and eighty-one subjects with a diagnosis of fibromyalgia were screened and one hundred and twenty four were randomized to receive paroxetine CR (dose 12.5-62.5 mg per day) or placebo for 12 weeks. Treatment response was defined as a 25% or greater reduction in scores on the Fibromyalgia Impact Questionnaire (FIQ) from randomization to end of treatment (LOCF). A blinded logistic regression analysis was conducted to determine the baseline variables that significantly predict treatment response.

Results: Overall response was 60% with a 29% drop out rate. The subjects were 93 % female, 63% Caucasian, 54% married, 63% employed with a mean age of 44 years. A diagnosis of current depressive disorders accounted for nearly 48% of the screen failures. About 40% of subjects had a comorbid diagnosis of Irritable Bowel Syndrome. Nearly 30% had a history of sexual abuse, and 25 % had a history of physical abuse. The blinded stepwise logistic regression model revealed a significant effect of history of sexual abuse ($p < .01$), however, there was no significant effect of history of physical abuse on overall response. Severity of symptoms, personality, sleep and pain disturbances, comorbid medical and psychiatric conditions, and level of disability were not predictive of response.

Conclusions: Depression and Irritable Bowel syndrome appear to be common comorbid conditions in fibromyalgia. Similar to many psychiatric disorders, a history of sexual abuse appears to predict poor response in fibromyalgia. A multivariate analysis of the data will be performed at the end of the study to examine the effect of study drug, and other clinical and demographic variables on treatment response.

Funding: GlaxoSmithKline

POSTER NO. 43

PREGABALIN IN GENERALIZED ANXIETY DISORDER: INFLUENCE OF DEPRESSIVE SYMPTOMS ON ANXIOLYTIC EFFICACY

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Objective/Background: To evaluate the anxiolytic efficacy of the novel alpha2-delta anxiolytic pregabalin in patients with clinically significant depressive symptoms.

Methods: The analysis sample consisted of patients from 5 double-blind, placebo-controlled 4-6 week trials of pregabalin for the treatment of DSM-IV GAD. The primary outcome measure was the Hamilton Anxiety Rating Scale (HAM-A). Effect size was calculated to compare the improvement in endpoint HAM-A scores for patients with a baseline HAM-D total score =15 (hi-dep) vs < 15 (lo-dep) across 3 treatment groups: pregabalin 150-200 mg (hi-dep, N=80; lo-dep, N=132), pregabalin 300-450 mg (hi-dep, N=164; lo-dep, N=276), and pregabalin 600 mg (hi-dep, N=107; lo-dep, N=210).

Results: Baseline clinical and demographic variables were similar across all treatment groups. For each of the three dosage ranges, in both hi-dep and lo-dep subgroups, pregabalin demonstrated significantly greater anxiolytic efficacy versus placebo. The average effect sizes for hi-dep versus lo-dep, respectively, were: pregabalin 150-200 mg, 0.44 versus 0.32; pregabalin 300-450 mg, 0.62 versus 0.38; pregabalin 600 mg, 0.50 versuss 0.41. All three pregabalin dosages were associated with significantly greater improvement in HAM-A total scores compared with placebo.

Conclusion: Pregabalin shows significant anxiolytic efficacy regardless of the presence of clinically meaningful comorbid depressive symptomatology.

Source(s) of Funding: Studies funded by Pfizer.

POSTER NO. 44

PREGABALIN'S PHARMACOKINETIC PROFILE SHOWS MINIMAL DRUG-DRUG INTERACTIONS

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Background/Objective: The pharmacokinetic properties of pregabalin, a novel alpha2-delta anxiolytic, were evaluated in a series of studies.

Method: A series of pharmacokinetic studies were conducted in healthy patients and in patients with renal disease to evaluate the effects of common clinical and demographic variables on pregabalin's pharmacokinetic parameters. Studies included single doses of =300 mg and multiple doses of =900 mg/d.

Results: Pregabalin showed rapid and dose-proportional absorption, with an absolute bioavailability of 90%, tmax of 0.7 to 1.5 h, and t½ of 6.3 h. Pregabalin does not bind to plasma proteins, it readily crosses the blood-brain barrier, and it is primarily renally excreted, 98% as unchanged drug. The lack of hepatic metabolism and of activity at CYP-enzymes resulted in an absence of pharmacokinetic effects in a series of drug-drug interaction studies. High-fat/heavy meals reduced the rate but not the extent of pregabalin absorption. Pregabalin's pharmacokinetics is not affected by gender or race, but it shows decreased clearance in the elderly, consistent with age-related changes in renal function, and in patients with renal impairment.

Conclusion: Pregabalin has a pharmacokinetic profile that suggests rapid onset of action with minimal risk of pharmacokinetic drug-drug interactions.

Source of Funding: Studies funded by Pfizer.

POSTER NO. 45

ATOMOXETINE AUGMENTATION FOR REFRACTORY ANXIETY DISORDERS

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Background: Though many patients achieve some response with the current pharmacotherapies for the anxiety disorders, most remain at least somewhat symptomatic and others respond not at all to initial therapy. We examined the effect of atomoxetine augmentation of anxiolytic pharmacotherapy in patients with anxiety disorders remaining symptomatic despite initial therapy.

Method: Retrospective chart review of 13 cases of augmentation with atomoxetine in adult outpatients who were not full responders to a variety of anxiolytic medications. Primary outcome measures were the Clinical Global Impression of Improvement and Severity Scales (CGI-I, CGI-S).

Subjects: Mean age of the subjects was 34 + 8 years. Patients had a range of anxiety disorders including Panic Disorder with Agoraphobia, Generalized Anxiety Disorder, Obsessive Compulsive Disorder and Social Phobia.
Results: The mean dose of atomoxetine was 77 + 36 mg/d, and the mean duration of treatment assessed was 8 + 5 weeks. Seven of 13 subjects (54 percent) were much or very much improved (CGI-I = 1 or 2) in terms of their anxiety symptoms, with the mean CGI-I = 2.5 + 1.0. The mean CGI-S at baseline was 5.8 + 0.6, which fell to 4.2 + 1.1 at endpoint ($t = 5.2$, $df = 12$, $p < .001$).

Conclusion: Results from this open retrospective case series, suggest that atomoxetine may effectively augment response to anxiolytic medications in patients with treatment-resistant anxiety disorders. Prospective, controlled studies are warranted to confirm these findings.

Disclosure: This work was funded by the Mood and Anxiety Disorder Institute of the Massachusetts General Hospital.

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POSTER NO. 46

SPEED OF ONSET OF PREGABALIN IN GENERALIZED ANXIETY DISORDER

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Objective/Background: The goal of this analysis was to evaluate the speed of onset of efficacy of the novel alpha2-delta anxiolytic, pregabalin.

Methods: Data were analyzed for doses ranging from 200 to 600 mg pregabalin from all placebo-controlled trials of pregabalin (including those with active comparators, alprazolam or venlafaxine) in DSM-IV GAD (total sample, N=868; female=60%; mean age=39 years; baseline HAM-A=26). Endpoints analyzed included sustained improvement in HAM-A total score at Week 1 that was significant at every visit thereafter using stringent a priori criteria and proportion of patients with early improvement (=30% reduction in HAM-A by Week 1).

Results: Significant and sustained Week 1 improvement was achieved with pregabalin, from the 200-mg dose (52%) to the 600-mg dose (54%) versus placebo (30%; $p<0.001$ for both comparisons). Significant early improvement was observed by Week 1 in both the HAM-A psychic and somatic factors. The active comparators, alprazolam and venlafaxine, were not statistically significantly different from placebo at Week 1.

Conclusion: Pregabalin demonstrated significant and sustained early onset of efficacy as early as Week 1 using stringent a priori criteria. The magnitude of early improvement was greater for pregabalin than either alprazolam or venlafaxine.

Source(s) of Funding: Studies funded by Pfizer.

POSTER NO. 47

FACILITATED EXTINCTION OF SOCIAL FEARS WITH D-CYCLOSERINE

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Objective/Background: Recent studies with D-cycloserine (DCS) appear to support its' potential to modify the amygdala pathology maintaining social phobias. The purpose of this study was to test the pro-extinction effects of an NMDA receptor/glycine site partial agonist, D-CS, in the treatment of patients with generalized social anxiety disorder (GSAD) undergoing brief cognitive behavioral therapy (CBT) based on Wells and Clark (1997) model.

Methods: The study is a double-blind, placebo-controlled, 3 group design comparing CBT/PLAC vs CBT/D-CS 50 mg po/day and CBT/D-CS 250 mg po weekly before CBT, in patients with GSAD. Patients received 6 weekly group CBT sessions followed by 2 biweekly sessions. Treatment outcomes were assessed by clinician ratings, self-report ratings, and behavioral assessment (a behavioral avoidance test and the Trier Social Stress Test).

Results: Thus far, 10 patients have completed the study. Mean percent improvement in Liebowitz Social Anxiety Scale scores (LSAS) was 48±26%. Mean±sd % LSAS improvement scores by treatment group were:
DC-250mg/week (n=3) =64±43%; DC-50mg/d (n=2)=31±2%; PLAC one cap/d (n=5)=44±15%. Similar trends were observed in the self-report and behavioral assessment measures. Gains were maintained at one month follow-up

Conclusion: High-dose intermittent D-CS administration may facilitate extinction of social fears in patients with established moderate - severe GSAD.

Source(s) of Funding: None

POSTER NO. 48

TIAGABINE IN GAD PATIENTS WHO WERE PARTIAL RESPONDERS TO SSRI THERAPY: AN OPEN-LABEL STUDY

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Objective/Background: Many patients with generalized anxiety disorder (GAD) who are treated with SSRI monotherapy may experience only a partial response. In these patients, augmentation with another agent may be appropriate. Gamma-aminobutryic acid (GABA), the primary inhibitory neurotransmitter of the CNS, plays a key role in the pathophysiology of anxiety. Tiagabine, a selective GABA reuptake inhibitor (SGRI) at the GAT-1 GABA transporter, increases synaptic GABA availability. Tiagabine has been shown to improve symptoms in patients with GAD., 1 The present study evaluated tiagabine as an augmentation therapy in patients with GAD who were partial responders to SSRI monotherapy.

Methods: This 8-week, open-label study evaluated tiagabine in patients with GAD who were partial responders (<50% reduction in objective or subjective assessment or rating scale) when on an adequate SSRI regimen (defined as =6 weeks on SSRI monotherapy on at least a minimally therapeutic dose, of which =4 weeks were at a stable dose). Patients were included if they had a HAM-A total score =16, Hospital Anxiety and Depression Scale, anxiety subscale score =7, and Clinical Global Impression of Severity score =4 at baseline. Tiagabine was initiated at 4 mg/d (2 mg bid, taken with food) and individually titrated weekly by 4 mg (2 mg bid) increments up to a maximum dose of 16 mg/d (8 mg bid). SSRI dosage was fixed throughout the study. Assessments included the HAM-A, and Clinical Global Impression of Change (CGI-C). Patients with at least 1 post-baseline, on-treatment efficacy.

Results: Forty-eight patients were enrolled and are included in the LOCF and safety analyses, of which 36 (75%) patients completed the study. Mean tiagabine dose was 10.2 (range 4-16) mg/d. Tiagabine improved symptoms of anxiety, as shown by a significant decrease from baseline at last visit in mean (±SD) HAM-A total score (20.7±3.6 vs. 11.3±7.4; P<0.001). At last visit, 25 (52%) patients were responders (=50% reduction from baseline in total HAM-A score) and 17 (35%) patients achieved remission (total HAM-A score =7). On the CGI-C, 27 (56%) of patients were responders ("much improved" or "very much improved"). The most commonly reported adverse events were somnolence (n=12) and dizziness (n=11). Four (8%) patients discontinued due to adverse events.

Conclusion: These preliminary results suggest that tiagabine may be an effective and generally well tolerated augmentation therapy in patients with GAD who are partial responders to SSRI monotherapy.

Source(s) of Funding: This study was sponsored by Cephalon, Inc., West Chester, PA.

Reference:

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POSTER NO. 49

DOUBLE BLIND PLACEBO CONTROLLED STUDY OF GENDER-BASED VARIABILITY IN NEURO-IMMUNOLOGICAL, NEURO-ENDOCRINE MEASURES WITH SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI) TREATMENT OF POSTTRAUMATIC STRESS DISORDER (PTSD)

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Objective/Background: PTSD is a chronic debilitating psychiatric illness. Medical co-morbids including coronary artery disease (1), musculoskeletal problems (2) and inflammatory diseases (3, 4, 5) are reported. Immune (6) and endocrine system (7, 8, 9) dysfunction may account for this. Gender difference in immunological variables in response to non-traumatic stressors is reported (10). We studied gender differences in interleukins and cortisol levels before and after SSRI treatment in PTSD subjects.

Methods: 58 adults with PTSD and 21 controls participated. Patients taking other psycho tropics or with substance abuse, serious medical illness, psychotic symptoms and any other primary Axis 1 diagnosis except depression or panic secondary to PTSD were excluded. Baseline Beck Depression Inventory (BDI), Clinician Administered PTSD Scale (CAPS), salivary am and pm cortisol levels, serum interleukin 1â (IL1â) and interleukin 2 receptors (IL-2R) were obtained for subjects and controls. We compared baseline means for all variables of subjects and controls with independent T-test. Subjects were randomized to double-blind sertraline (n=18), 20-50 mgs/day; citalopram (n=19), 50-200 mgs/day or placebo (n=7) for 10 weeks. We obtained end BDI and CAPS scores, am and pm cortisol, IL1â and IL-2R for subjects. . ANOVA compared post-treatment variables for three treatment groups. Pooled females (n=43) and males (n=15) were compared at baseline by using 2-sample independent T tests. At exit, we compared difference between baseline and delta values in variables for pooled males and females using 2-sample independent T test.

Results: At baseline, randomized PTSD subjects had higher IL1â (p=<. 0001), CAPS (p=<.0001), BDI (p=<.0001), and lower IL-2R (p=< .0001) than controls. Differences in am and pm cortisol were not significant. Pooled males and females did not show significant differences at baseline. After treatment, three groups did not differ from each other in psychometric, cortisol or IL measures. With treatment, significant changes in IL1â (p=<.0001), IL-2R (p=<.0001), CAPS (p=<.0001), BDI (p=<.0001) were observed. Am and pm cortisol did not change significantly. Both IL1â (120.35 vs. 59.02 in controls) and IL-2R (411.91vs 645.16 in controls) achieved levels of controls. For these variables both at baseline and in delta values, there were no statistical difference between pooled females and males.

Conclusion: No gender differences were found in any of the variables either at baseline or in delta values. Post-treatment IL values for all three-treatment groups containing both genders were comparable with values for controls at baseline, indicating normalization. Further studies with larger sample sizes are needed.

Source(s) of Funding: Forest Pharmaceuticals, Inc.

POSTER NO. 50

ATYPICAL ANTIPSYCHOTICS AND RECEPTOR BINDING: ENHANCING COGNITION AND MOOD

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Objective: Schizophrenia is characterized by a diversity of symptoms that hypothetically arise from heterogeneous neuroanatomical and neurochemical malfunctions. This review will profile the unique portfolio of receptor binding actions for each of the five first-line atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) and discuss the theoretical implications these binding properties hold for potential efficacy in improving cognition and mood in schizophrenia.

Methods: Articles characterizing receptor binding properties of atypical antipsychotics were selected by means of search in MEDLINE.

Results: All antipsychotic agents target the key hypothetical neurochemical disturbance in psychosis-excessive dopamine neurotransmission at dopamine-D2 receptors in the mesolimbic pathway of the brain-presumably responsible for the positive symptoms of schizophrenia. All atypical antipsychotic agents are serotonin-2A (5-HT2A)/dopamine-D2 antagonists or D2 partial agonists; properties that contribute to reduced motor side effects. Interaction with 5-HT2C, 5-HT1D, and 5-HT1A receptors, and serotonin and norepinephrine reuptake sites, in human brain tissue predict cognitive improvement, heightened negative symptom relief, and enhanced modulation of mood. Affinity for a1-adrenoceptors, histamine H1 receptors and muscarinic M1 receptors predicts orthostatic hypotension, sedation, cognitive disturbance, or weight gain.

Conclusions: Receptor binding properties other than serotonin-2A/dopamine-D2 occupancy may explain cognitive and affective symptom improvement associated with atypical antipsychotic therapy.

Source of Funding: Supported by funding from Pfizer, Inc.

POSTER NO. 51

A MOLECULAR-GENETIC APPROACH TO MODELING PSYCHOTROPIC DRUG RESPONSE

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Objective/Background: Currently available drug treatments for affective disorders are insufficient, mainly because the mechanisms underlying the various classes of antidepressants are not well understood. In fact, a recent analysis of FDA data on 10'030 patients from 52 antidepressant drug trials has revealed that active substances showed superiority to placebo in fewer than half of the studies, while symptom reduction was 47.9% with investigational drugs, 47.5% with established active comparators, and 35.5% with placebo. And, what is really puzzling: (1) antidepressants that differ greatly in their biochemical and pharmacological actions have virtually the same efficacy in terms of the proportion of patients in whom they induce a therapeutic response, (2) a large proportion of patients (35%-45%) have a refractory depression with an insufficient response to many or even all drug treatments, (3) a large proportion of moderately to severely depressed patients (30%-40%) are placebo responders, (4) patients do not necessarily respond to the same drug in multiple episodes, (5) some patients show immediate improvement under antidepressants while others suffer from a delayed onset of action, (6) antidepressants appear to be polyvalent in the sense that they induce a therapeutic response under various clinical indications. Specifically, it is currently impossible to make any predictions of whether or not a particular patient will respond to a particular treatment.

Methods: To search for genetic factors that control response to psychotropic drug treatment, we have carried out a molecular-genetic pilot study on 257 patients genotyped for 72 candidate genes. The time characteristics of recovery were determined for each individual patient through survival-analytical methods on the basis of the "HAMD-17" and "PANSS" rating scales. The resulting quantitative phenotype was then correlated with oligogenic configurations of genomic loci.

Results: Using 105 patients treated with SSRIs (paroxetine) as calibration samples, we found a configuration of 23 genomic loci having a highly significant correlation with the phenotype, thus enabling the discrimination between "early"-, "late"-, and "non"-improvers at a rate of >75% correctly classified patients. Applied to our independent replication sample of 152 patients treated with neuroleptics (risperidone), the same configuration of 23 genomic loci yielded 85.4% correctly classified "early"- and 65.9% correctly classified "late" improvers.

Conclusion: Response to psychotropic drug treatment appears to be to a substantial part determined by an unspecific "recovery-genetic" component which is independent of treatment modality and can be triggered by various exogenous and endogenous factors. A much smaller "pharmaco-genetic" component causes the variation in dose, blood level, and side effects.

Source(s) of Funding: Supported in part by a grant of the Swiss National Science Foundation (SNF 31-63769.00)

POSTER NO. 52

DRUG TREATMENT PATTERNS OF BIPOLAR DISORDER AND ASSOCIATED COSTS

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Background: Pharmacotherapies are effective in mood stabilization and episode prevention in patients who have bipolar disorder. Current clinical guidelines strongly recommend long-term preventive pharmacotherapy for the management of bipolar patients. This study profiles drug treatment patterns for bipolar patients and compares costs associated with patients in alternative treatment groups.

Methods: The study sample was drawn from a de-identified administrative claims database of approximately 1.8 million beneficiaries from 1999 to 2002, which included medical, drug, and disability claims. Patients aged 18 to 65 years who had at least 2 bipolar diagnoses, or 1 bipolar diagnosis and at least 1 prescription for a mood stabilizer, were included (N=3499). The intent-to-treat approach was adopted to profile the treatment patterns using drug and medical claims in the 2 months following the initial diagnosis. Costs were measured from an employer's perspective and adjusted to 2002 dollars using appropriate Consumer Price Indices. *t*-Tests were conducted to estimate statistical significance.

Results: Forty-five percent of patients received no specific drug treatment for bipolar disorder in the first 2 months following the diagnosis. Within this "no-specific-treatment" group, 65% received psychotherapy and 35% received no specific bipolar treatment; however, 62% received antidepressants, which are contraindicated by clinical guidelines. Of the 55% of patients treated with bipolar-specific drugs, 91% took mood stabilizers in the first 2 months after diagnosis. Conventional antipsychotics were rarely used, and atypical antipsychotics were usually taken in combination with mood stabilizers. After the first observed bipolar episode, patients on mood stabilizer monotherapy incurred increases in medical costs (36%) and drug costs (59%), and a slightly decrease in work-loss costs (-5%), whereas patients on atypical antipsychotics had a decrease in medical costs (-17%), an increase in drug costs (66%), and a decrease in work-loss costs (-13%). On average, therapy with atypical antipsychotics could have saved $4796 annually, reflecting a decrease of $4640 in medical costs, an increase of $158 in drug costs, and a decrease of $314 in work-loss costs compared with mood stabilizer monotherapy.

Conclusions: Patients with bipolar disorder were often untreated or treated inappropriately (with antidepressant monotherapy). Appropriate combination therapy with atypical antipsychotics and a mood stabilizer may potentially reduce both direct health care costs and indirect work-loss costs.

Funding Source: The research presented was supported by AstraZeneca Pharmaceuticals LP.

POSTER NO. 53

ANTI-ANXIETY EFFECTS ANALYSIS OF QUETIAPINE IN BIPOLAR DEPRESSION

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Objective: Evaluate efficacy and safety of quetiapine monotherapy for anxiety symptoms in patients with bipolar depression.

Method: 511 patients (342 bipolar I, 169 bipolar II depression) who received 8 weeks double-blind treatment with quetiapine (300 or 600 mg/d) or placebo were included in the efficacy analysis. Anxiety symptoms were assessed using the Hamilton Rating Scale for Anxiety (HAM-A).

Results: Mean baseline levels of anxiety measured by HAM-A score were similar across treatment groups: 18.6 - 18.9. Patients taking quetiapine 300 and 600 mg/d had significantly ($P<0.05$) greater improvement in mean HAM-A score vs placebo at every assessment starting with the first evaluation (Day 8) and sustained through endpoint (Week 8) (-8.6 and -8.7 vs -5.5). Common quetiapine adverse events (>10% and $\geq$2x placebo rate) were dry mouth (43%), sedation (31%), somnolence (26%), dizziness (20%), and constipation (11%).

Conclusions: Quetiapine monotherapy (300 or 600 mg/d) is significantly more effective than placebo and well tolerated for the treatment of anxiety symptoms in patients with bipolar depression.

Source(s) of funding: This research was supported by AstraZeneca.

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POSTER NO. 54

PRELIMINARY RESULTS ON PREGNANCY OUTCOMES IN BIPOLAR WOMEN: DATA FROM THE LAMOTRIGINE PREGNANCY REGISTRY

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Objective/Background: Pregnancy presents a special problem to the clinician treating bipolar disorders in women. In 1992, the International Lamotrigine Pregnancy Registry was initiated to monitor pregnancies for the occurrence of major birth defects among women exposed to lamotrigine (LTG) during their first trimester. LTG has been monitored for the past 10 years for epilepsy, bipolar disorders, and other conditions. This report provides a summary of event rates among bipolar women, as of September 2003, to estimate the safety of LTG use in pregnancy.

Methods: The registry is an observational, follow-up study designed to detect evidence of teratogenicity. To date, n= 684 of pregnancies have been enrolled anonymously by health care providers. Pregnancy-outcome ascertainment was obtained through subsequent follow-up with the reporting health care provider, and an expert pediatrician reviewed each reported birth defect. An advisory committee of independent scientists reviewed. In this report, we describe the characteristics of women using LTG in early pregnancy and the rate of major congenital abnormalities among bipolar women.

Results: Pregnancies among bipolar women were approximately 3% of the total number enrolled in the registry (18/684). Nearly 78% of the women were white (14/18) and 15 (83%) were from US. Pregnancy exposures for all 18 bipolar women occurred during the first trimester. Outcomes of these pregnancies were live-born infants without birth defects in 89% (16/18) and legal induced abortions in 11% (2/18). Maternal age ranged from 16 to 35 years, with a mean age 28.61±5.10 years. Ten women (55.6%) were older than 29, 7 (38.9%) 20-29 years of age, and 1 (15.6%) younger than 20 years. Twelve of women received Lamotrigine monotherapy. Politherapy was mainly with antidepressants and antiepileptics (66%). Among the live-born infants, 56% were female, 75% (12/16) were gestational aged between 38-41 weeks, and exhibited a mean birth weight of 3678 SD ? 530 gms. The observed proportion of major defects in bipolar woman was 0% (0/18). No specific patterns of major birth defects in any subgroup or within the registry as a whole were observed.

Conclusion: Although, there were too few pregnancy outcomes among bipolar women to reach definitive conclusions about the possible teratogenic risk of this drug, the data from this registry have found no evidence of any adverse pregnancy outcome associated with LTG use in bipolar women. Data obtained through these registries are shared with the medical community as a supplement to animal toxicology studies to assist in weighing potential risks and benefits of treatment for individual patients. The success of the registries depends on the continued willingness of the psychiatrics, and obstetrics community to notify the registries of prenatal exposures.

Source(s) of Funding: GlaxoSmithKline

POSTER NO. 55

ARIPIPRAZOLE FOR RELAPSE PREVENTION IN A 26-WEEK PLACEBO-CONTROLLED TRIAL IN BIPOLAR DISORDER

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Objective: To compare aripiprazole with placebo in the maintenance of stability of patients with bipolar I disorder in a 26-week, double-blind relapse prevention study.

Methods: Patients who had recently experienced a manic or mixed episode, entered a stabilization phase receiving open-label aripiprazole 15-30 mg/day (starting dose = 30 mg/day), for 6-18 weeks. After meeting stabilization criteria (Y-MRS=10 and MADRS=13 for 4 consecutive visits or 6 weeks), 161 patients were randomized to aripiprazole or placebo for the 26-week maintenance phase. The primary endpoint was time to relapse of manic, mixed, or depressive symptoms, defined as discontinuation due to lack of efficacy (hospitalization for manic or depressive symptoms, or requiring a dosing change in psychotropic medications other than study drug).

Results: Time to relapse of symptoms was significantly prolonged with aripiprazole compared to placebo (p=0.020). Total number of relapses (manic, mixed, or depressive symptoms) were significantly fewer in patients treated with aripiprazole than placebo (25% vs. 43%, p=0.013). The only adverse events (=10% incidence) more common than placebo were anxiety and nervousness.

Conclusion: Aripiprazole prolongs time to relapse of symptoms in stabilized patients with bipolar I disorder who previously experienced a manic or mixed episode.

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POSTER NO. 56

ZIPRASIDONE IN BIPOLAR MANIA: EFFICACY ACROSS PATIENT SUBGROUPS

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Objective: To evaluate the efficacy of ziprasidone in bipolar mania, focusing on clinically relevant subgroups.

Methods: This was a secondary analysis of 2 randomized, double-blind 21-day trials comparing flexible-dose ziprasidone (40-80 mg BID) to placebo in adults with mania associated with bipolar I disorder. Changes in Mania Rating Scale (MRS) and CGI-S were calculated for combined study populations and in subgroups of patients with manic episodes, mixed episodes, and with or without psychotic symptoms.

Results: Mean daily dose was approximately 120 mg. At last visit (LOCF), mean change in MRS in patients receiving ziprasidone (n=268) was -11.72 (baseline 26.82) versus -6.69 (baseline 26.53) in patients receiving placebo (n=131) ($p<0.001$). Change in CGI-S for ziprasidone was -1.19 (baseline 4.71) versus -0.66 (baseline 4.76) for placebo ($p<0.001$). Significant improvement versus placebo was observed from Day 2 for MRS and Day 4 for CGI-S. The 95% confidence intervals for placebo-corrected LS mean change from baseline in all patients and in the four subgroups (manic, mixed, and with and without psychotic symptoms) overlapped, indicating comparable efficacy.

Conclusions: Ziprasidone rapidly improves symptoms and global illness severity in bipolar mania and is efficacious in mixed and manic episodes and in presence or absence of psychotic symptoms.

Source of Funding: Supported by funding from Pfizer Inc.

POSTER NO. 57

DONEPEZIL IN BIPOLAR DISORDERS WITH COGNITIVE IMPAIRMENT/ DEMENTIA

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Background: Cognitive impairment and dementia can be noted in manic and bipolar disorder patients in late life. Although the nature of such overlap with mood disorder is not clear, patients with these impairments may be appropriate for treatments such as cholinesterase inhibitors. Furthermore, cholinergic augmentation reportedly can have anti-manic effects. We reviewed clinical use of adjunctive cholinesterase inhibitor treatment in a series of older adult patients with bipolar disorder or schizoaffective disorder, bipolar type.

Methods: Clinical records of patients of a university-based geropsychiatry service were reviewed. Patients with bipolar disorder or schizoaffective disorder, bipolar type who were treated with donepezil were identified.

Results: Eight (n=8) patients reviewed had a mean age of 73.6 years. They were all female. Four had mild cognitive impairment and four had co-morbid dementia. In six patients, donepezil was initiated during management for manic episode; in two, it was added when their manic symptoms had remitted. All patients were also receiving pharmacotherapy for their mood disorders. In two cases the final donepezil dose was 10 mg/day; the remainder were treated with 5 mg/day. One patient complained of nausea at 10 mg/day but not after dose reduction to 5 mg/day. The maximum duration of donepezil treatment assessed in this sample was 6 months. No exacerbation or activation of affective psychopathology was noted.

Conclusions: This preliminary experience suggests that cholinesterase inhibitor treatment can be adequately tolerated in elders with BP disorder.

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POSTER NO. 58
INITIAL SYMPTOMS OF MANIC RELAPSE

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Objective/Background: To identify manic symptoms as early predictors (within 2 weeks) of manic relapse in a double-blind, randomized relapse prevention study of olanzapine versus lithium.

Methods: Post hoc analysis of Young Mania Rating Scale (YMRS) items prior to episodes of manic relapse (YMRS >15 or hospitalization) was conducted using bi-weekly data from 398 initially euthymic (YMRS <=12) patients with bipolar I
disorder randomized to olanzapine (OLZ, n=199, 5-20 mg/day) or lithium (Li, n=199, serum level of 0.6 to 1.2 mEq/L). Relapses were captured for the first 3 to 16 weeks after randomization. Repeated-measures logistic regression analysis of detectable changes in clinical symptoms (increase in an item score of 1 or more) during the 2 weeks prior to relapse was used to estimate odds of relapse by the next visit.

Results: A total of 32 subjects relapsed within this study period (OLZ, n=15; Li, n=17, respectively). YMRS scale items that increased most frequently preceding manic relapses (OLZ vs Li, respectively) were: increased motor activity/energy (46.6%, 17.7%), decreased need for sleep (26.7%, 17.7%), irritability (20.0%, 17.7%), and rapid speech (20.0%, 17.7%). YMRS scale items with largest odds ratios for predicted relapse were: increased motor activity/energy (14.1, p<.001), disheveled appearance (9.2, p=.021), and irritability (7.24, p=.002) in
olanzapine-treated patients, and disruptive-aggressive behavior (6.9, p=.022) in lithium-treated patients. Overall, 73.3% olanzapine-treated vs. 58.8% lithium-treated patients had pre-relapse increases in at least one YMRS scale item.

Conclusion: Increases in manic symptoms two weeks prior to relapse were found more often with
olanzapine- than lithium-treated patients. Early detection of these symptoms may permit clinical interventions to help avert relapse.

Source(s) of Funding: Eli Lilly and Company

POSTER NO. 59

EFFICACY AND SAFETY OF ZIPRASIDONE IN BIPOLAR DISORDER: LONG-TERM DATA

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Objective: To evaluate efficacy and tolerability of long-term ziprasidone treatment in patients with bipolar disorder.

Methods: We analyzed primary results from a 2-year open-label extension of a 21-day placebo-controlled trial of ziprasidone in mania associated with bipolar I disorder. Efficacy assessments were performed at day 3 and weeks 1, 2, 4, 12, 28, 52, 76, and 104. Observed cases and last visit (LOCF) analyses were conducted.

Results: The extension enrolled 127 patients. Mean dosage was 122.4 mg/d. A Kaplan-Meier survivor estimate found 50% of patients remained in the study at day 100 and 30% after 1 year. Scores on the Mania Rating Scale and CGI-S, the primary efficacy variables, continued to improve from extension baseline up to week 12, with improvement sustained at weeks 28, 52, 76, and 104, and last visit. Concomitant medications included anxiolytics (77.9%), hypnotics and sedatives (41.7%), antiepileptic drugs (29.9%), antidepressants (27.6%), and lithium (14.1%). Ziprasidone was well tolerated; 15 (11.8%) patients discontinued due to treatment-related adverse events. Fourteen (12.5%) patients had weight gain =7% and 20 (17.9%) weight loss =7%.

Conclusion: Ziprasidone is associated with long-term symptom and global improvement in patients with bipolar I disorder and is well tolerated, with a weight-neutral profile.

Source(s) of Funding: Supported by funding from Pfizer Inc.

POSTER NO. 60

FLUOXETINE MONOTHERAPY OF BIPOLAR TYPE II MAJOR DEPRESSION - LACK OF MANIC INDUCTION

Justine Shults

Objective/Background: There is a paucity of controlled data on the treatment of BP II Major Depressive Episode (MDE). Concern over manic switch episodes during antidepressant monotherapy (ADM) has impeded the development of effective short-term therapies of BP MDE. Prior studies by our group suggest that SSRIs may be a safe and effective initial therapy for BP II MDE with a low manic switch rate. The objectives of the present study are to determine: 1) Is SSRI ADM an effective initial treatment of BP II MDE? and, 2) Is SSRI ADM associated with a low manic switch rate in BP II MDE patients?

Methods: As part of a long-term, relapse-prevention study, 71 BP II MDE patients (44 women), age 19-76 years, with a Hamilton Depression Rating (HAM-D17) score 16 were treated with open-label fluoxetine 10-80 mg daily for up to 10 weeks. HAM-D17, Clinical Global Impression (CGI/C), and Young mania ratings (YMR) measures were obtained at weeks 1, 2, 4, 6, 8, and 10.

Results: 38% of patients remitted with a final HAM-D17 score ¡Ü8 and 76% responded with a ¡Ý50% reduction in baseline HAM-D17 score by week 10 of ADM. An ITT analysis using LOCF data showed a significant reduction in HAM-D17 scores by week 6 ($p<0.0005$). Generalized Estimating Equation (GEE) analysis of YMR scores was used to assess ADM-induced manic symptoms at each study visit (vs. baseline). No significant differences in YMR scores were observed during ADM ($p = 0.21$).

Conclusion: These preliminary data support earlier findings that SSRI ADM may be a safe and effective initial therapy of BP II MDE with a low manic switch rate.

Source(s) of Funding: NIH grant #R01 MH 060353

POSTER NO. 61

EARLY WEIGHT GAIN AS A PREDICTOR OF SUBSTANTIAL WEIGHT: RESULTS FROM SEVEN STUDIES OF OLANZAPINE FOR THE TREATMENT OF BIPOLAR DISORDER

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Objective/Background: Atypical antipsychotics are being used as mood stabilizers for treatment of bipolar disorder. Weight gain, sometimes substantial, is observed during treatment with some of the atypical agents. The objective was to examine early weight gain (EWG) during olanzapine (OLZ) treatment as a predictor of substantial weight gain (SWG) later in treatment.

Methods: Data were pooled from seven randomized, multicenter studies in bipolar patients (N=2231 at initiation of olanzapine). Endpoint for this analysis was 32 weeks (n=518). SWG was defined as gaining at least 10 kg at endpoint. Other definitions of SWG (5 and 7 kg) were also evaluated. EWG was determined as the weight gain threshold that optimized discrimination of patients with SWG.

Results: At an EWG threshold of about 2 kg in the first 3 weeks, among patients with SWG 61% also had EWG (sensitivity), and 69% of patients without SWG did not have EWG (specificity). Among those patients who did not have EWG, 83% did not have SWG. Addition of baseline characteristics (including age, gender, baseline body mass index, non-white race) moderately improved predictability. Results for other SWG cut-offs were qualitatively similar.

Conclusion: EWG of about 2 kg during first 3 weeks of treatment with OLZ predicted later SWG. Patients with lesser EWG appeared much less likely to have SWG. Further research in larger patient populations and for longer time periods is necessary to explore the predictive power of EWG for SWG with olanzapine as well as other medications, particularly in patients with symptomatic bipolar disorder.

Source(s) of Funding: Eli Lilly and Company

POSTER NO. 62

VARYING THE CRITERIA FOR RESPONSE AND REMISSION IN BIPOLAR DEPRESSION

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Objective/Background: Varying the criteria used to determine response and remission in antidepressant clinical trials can alter the results substantially. Although certain criteria are commonly used (e.g., =50% decrease in depression score for response), there are as yet no standardized definitions for response or remission1. The purpose of this analysis was to examine the patterns of response and remission rates in a clinical trial of olanzapine/fluoxetine combination (OFC), olanzapine, and placebo for bipolar depression when different criteria for response and remission are used.

Methods: Acute phase Montgomery-Åsberg Depression Rating Scale (MADRS) data from a double-blind, placebo-controlled, randomized clinical trial comparing OFC (n=82), olanzapine (n=351), and placebo (n=355) for bipolar depression were analyzed. Response and remission rates were calculated for the three therapies based on various endpoint criteria for response (=25%, =50%, and =75% decrease in MADRS total score) and remission (MADRS total score =12, =10, =8, and =6).

Results: Percentages of subjects responding at the level of =25% MADRS total score improvement at endpoint were 80% for OFC, 63% for olanzapine, and 52% for placebo. Using a criterion of =50% MADRS improvement, response rates were 60%, 42%, and 34% for OFC, olanzapine, and placebo, respectively. With a criterion of =75% MADRS improvement, response rates were 32%, 21%, and 15%, respectively. Remission rates using a criterion of endpoint MADRS =12 were 50%, 34%, and 27% for OFC, olanzapine, and placebo, respectively. For endpoint MADRS =10, remission rates were 46%, 26%, and 22%, respectively. For endpoint MADRS =8, remission rates were 38%, 21%, and 17%, respectively. For endpoint MADRS =6, remission rates were 29%, 16%, and 14%, respectively.

Conclusion: The three therapy groups demonstrated similar patterns of results for response and remission regardless of the criteria used. Patients treated with OFC consistently had response and remission rates higher than olanzapine or placebo, and nearly one-third of OFC patients met the most stringent criteria for response (=75% MADRS improvement) and for remission (MADRS =6).

Source(s) of Funding: Eli Lilly and Company

POSTER NO. 63

SERUM LEVEL CHANGES ASSOCIATED WITH SWITCHING PSYCHIATRIC PATIENTS FROM A DELAYED-RELEASE TO AN EXTENDED-RELEASE FORMULATION OF DIVALPROEX SODIUM

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Objective/Background: Divalproex sodium extended release (ER) formulation (Depakote-ER) has become available for use and is being prescribed for patients with bipolar disorder. There are as yet no established guidelines for dosage conversion from "DR" (delayed release) to "ER" as serum levels on equivalent doses have not been assessed. This study evaluated the serum valproic acid levels in a small group of patients switched from divalproex sodium DR to divalproex sodium ER.

Methods: Divalproex sodium dosage and serum levels were reviewed retrospectively for 16 patients with bipolar illness who switched from divalproex sodium delayed release to extended release; 9 patients had complete serum level data for each formulation. DR: ER conversion ratios ranged from 1: .67 to 1: 1.5 (see table). Valproic acid serum levels in all patients were in the therapeutic range at the time of the formulation switch. Serum levels were obtained after reaching steady state (DR range 7-72 days after last dosage adjustment; dosage range 600-1500 mg/day) (ER range 6-68 days after last dosage adjustment; dosage range 500-2000 mg/day) with specimens obtained 10-15 hours after dosage.

Results: Mean valproic acid serum levels were 81.89 mcg/ml +/- 16.95 while at steady state on the DR formulation, and 84.0 mcg/ml +/- 20.9 when at steady state on the ER formulation. Post-switch, all patients but 1 were within therapeutic plasma serum levels (including the two patients with serum level increases) and within 10% of their DR plasma serum level regardless of DR:ER dosing conversion ratio. A reduction in serum level was seen with the 1: .67 conversion.

Conclusion: Converting from DR to ER in this small sample of bipolar subjects resulted in continued therapeutic levels of divalproex sodium in all patients with 1:1, 1.2 or 1.5 conversion ratios. A decrease in dose from DR to ER resulted in a decreased serum level. Dosing conversion algorithms should be developed and should include 1:1 ratios or greater. The qd (qhs) dosing of ER may result in enhanced compliance, but serum levels should be checked after ER steady state is reached.

Source(s) of Funding: Funding provided by Abbott Laboratories for data analysis; original data gathered for NIH study 1 R01 MH57762. Dr. Altshuler receives funding from Abbott Laboratories for research and consultation. Dr. Levander receives research fellowship funding from Abbott Laboratories.

POSTER NO. 64

PHENOCHIPPING OF PSYCHOTIC DISORDERS: A NOVEL APPROACH FOR DECONSTRUCTING AND QUANTITATING PSYCHIATRIC PHENOTYPES

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Objective/Background: Psychiatric phenotypes as currently defined are the result of clinical observation and consensus criteria rather than empirical research. We propose and present initial proof of principle for a novel approach, termed PhenoChipping, by analogy with, and borrowing paradigms from, gene expression microarray studies (GeneChipping).

Methods: Massively parallel sampling of the mental state is done with a PhenoChip composed of a battery of existing (PANSS, HAM28, YMRS, SFGEN36) and one new (SMS- Simplified Mood Scale) psychiatric rating scale, as well as neurophysiological motor measures (hand velocity scaling, force instability) in 113 subjects, 78 with psychotic disorders and 35 normal controls.

Results: Our quantitative mood state scales (SMS) accounts for a significant portion of the variability captured by more complex existing rating scales for not only mood (HAM28, YMRS), but also psychosis (PANSS). Objective motor measures show correlation with phenotypic items both cross-sectionally and in repeat measures. The motor measures display left vs. right hand differences in scores that may reflect hemispheric lateralization of the correlated pathophysiology.

Conclusion: We propose that PhenoChipping uncovers new relationships between phenotypic items ("phenes"). This generative, empirical approach will be of use in helping move us beyond current classifications of mental illness, toward clusterings that may better serve research and clinical practice.

Source(s) of Funding: NARSAD Young Investigator Award (ABN) NIMH R01-MH-57140 (JBL)

POSTER NO. 65

A LONGITUDINAL 7-YEAR FOLLOW-UP STUDY OF BIPOLAR DISORDER IN A UNIPOLAR COHORT

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GlaxoSmithkline

Objective/Background: Bipolar disorder is widely misdiagnosed as unipolar depression which leads to inappropriate treatment and a more severe course of illness. This study will provide real-world population data that estimates how often bipolar disorder merges after a diagnosis of unipolar depression. The information from this study will form a basis for improving primary care physican recognition of bipolar symptoms. Follow a cohort of patients that have been diagnosed with Major Depression and measure the occurrence of a subsequent Bipolar Disorder diagnosis. In order to determine patient factors that may predict this misdiagnosis, we will compare baseline patient characteristics and comorbid conditions between those that "switch" from unipolar to bipolar depression and those that do not. Compare patient and treatment characteristics following a unipolar diagnosis in order to identify clinical features that may differentiate those that "switch" from unipolar to bipolar depression and those that do not.

Methods: IMS LifelinkTM is an integrated employer claims database, with health care experience of roughly 1.8 million individuals. The database contains medical and pharmacy claims beginning in 1994 to 2001. 11,517 patients initially diagnosed with unipolar depression were followed for 7 years.

Results: The incidence of bipolar disorders in this unipolar cohort was 1.7% (n= 1,013). Significant differences emerged in age at with an incidence of 5.7 % in younger patients (18-34 years) compared with 3.8% in 35-54 y.o patients and 2.5% in >= 55 y.o. Unipolar depressed patients were significantly more likely than bipolar patients to present more diabetes, cardiovascular diseases and neoplams. Those with histories of substance abuse showed a significantly higher rate of switching to bipolar illness (incidence 5.0% vs. 1.7%). Patients with initially bipolar disorder (n=2,057) were more likely to have psychiatric hospitalizations, ER visits and use of more than 2 psychiatric medications.

Conclusion: Young patients with diagnosis of unipolar depression and history of substance abuse may be at especially high risk for eventually developing bipolar disorder. This analysis highlights the need for greater attention to recognizing those at high risk for under-diagnosis or misdiagnosis of BP disorder.

Source(s) of Funding: GlaxoSmithKline

POSTER NO. 66

THE PREVALENCE OF BIPOLAR DISORDER AND COMORBID DISORDERS IN A SAMPLE OF OTTAWA COUNTY JAIL INMATES

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Objective/Background: To assess the prevalence of Bipolar Disorder and its comorbidity in jail inmates.

Methods: During booking, each inmate completes the Mood Disorder Questionnaire (MDQ) and Michigan Alcohol Screening Test (MAST). Researchers then interview every consenting inmate and obtain demographic information, administer the MINI International Neuropsychiatric Interview (MINI), the alcohol/drug sections of the Structured Clinical Interview for DSM-IV (SCID), and the Addiction Severity Index.

Results: Sixty-nine inmates consented to be interviewed. Seventy-five percent of the consenting sample had a negative MDQ score. The prevalence rates assessed using the MINI and SCID are: 41% for Bipolar Disorder, of which 86 % is Bipolar I disorder. The rate of comorbid anxiety disorders is 75%. The rate of comorbid substance use disorders in inmates with Bipolar Disorder is 93%. In the dually diagnosed bipolar sub-sample, the lifetime pattern of substance use disorders was the following: 93%with alcohol use disorders, 56% with cannabis use disorders, 30% with cocaine use disorders, 37% with other substance use disorders. Fifty-nine percent of that sub-group had two or more substance use disorders, while 44% had 3 or more substance use disorders. The rate of anxiety disorders in the dual-diagnosis sub-sample is 70% including: 56% with Post Traumatic Stress Disorder, 33% with Generalized Anxiety Disorder, 26% with Panic Disorder, 7% with Social Anxiety Disorder, and 7% with Obsessive Compulsive Disorder. Of those who qualified for a diagnosis of Bipolar Disorder, 39% had previously been correctly diagnosed. The mean delay in receiving a correct diagnosis for Bipolar Disorder since the onset of symptoms is 15 years.

Conclusion: A high prevalence rate of BD is observed in this inmate sample. The majority of inmates with BD present comorbid with either substance use disorders or anxiety disorders. Most of the cases are undiagnosed and untreated. The recognition and treatment of this population remain important public health issues that need to be further addressed.

Source(s) of Funding: HRSA, HHS.

POSTER NO. 67

TIME IN EUTHYMIA FOR BIPOLAR PATIENTS RECEIVING OLANZAPINE OR LITHIUM MAINTENANCE TREATMENT

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Objective/Background: In evaluating maintenance therapies for bipolar disorder, it is important to consider not only time to relapse but also time in euthymia. The following post-hoc analyses compared time in euthymia for patients receiving olanzapine versus patients receiving lithium.

Methods: 543 patients with a diagnosis of bipolar I disorder, manic or mixed type, with a history of at least 2 manic or mixed episodes within 6 years, and a Young Mania Rating Scale (YMRS) total score >=20, entered the study and received open-label combination therapy of olanzapine and lithium for 6-12 weeks. Of these, 431 patients met symptomatic remission criteria (YMRS total score <=12 and Hamilton Depression Rating [HAMD-21] total score <=8) and were randomized to monotherapy with either olanzapine (N=217) (5-20 mg/d) or lithium (N=214) (titrated to a therapeutic serum level of 0.6 to 1.2 mEq/L in a dose range of 300-1800 mg/d) for 12 months of double-blind treatment. Time in euthymia was defined as the number of days that a patient remained in remission and free of any subsyndromal symptoms (YMRS of 13 or 14; HAMD of 9 to 14) during the double-blind period.

Results: Patients receiving olanzapine maintenance treatment remained in remission, free of subsyndromal symptoms, for a median of 241 days. Patients receiving lithium maintenance treatment remained in remission for a median of 177.5 days (Wilcoxon P=.26). Patients receiving olanzapine remained free of subsyndromal manic symptoms for a median of 250 days compared with 186 days (P=.34) for lithium patients. Olanzapine patients remained free of subsyndromal depressive symptoms for a median of 241 days compared with 177.5 days (P=.27) for lithium patients. In general, subsyndromal symptoms for either treatment group occurred relatively infrequently, with only 19.8% of olanzapine patients and 21.5% of lithium patients experiencing subsyndromal symptoms. Time in euthymia accounted for 95% of patients' time in both treatment groups.

Conclusion: Olanzapine monotherapy was similar to lithium monotherapy in terms of patients' median number of days in euthymia, and subsyndromal symptoms accounted for a small amount of patients' time while in the study.

Source(s) of Funding: Eli Lilly and Company

POSTER NO. 68

A COMPARISON OF THE EFFICACY AND SAFETY OF QUETIAPINE AND DIVALPROEX SODIUM IN THE TREATMENT OF ACUTE MANIA

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Objective/Background: Divalproex sodium (valproic acid; VPA), an approved treatment for bipolar mania, has been shown to reduce symptoms when initially administered at high doses. Quetiapine has also been shown to alleviate mania symptoms rapidly, but concerns exist about whether the dosage can be increased safely.
A 2-week, randomized, rater blinded study compared the safety and efficacy of escalating doses of quetiapine administered over 4 days on a three times daily. basis with VPA in adults with acute mania.

Methods: Patients hospitalized for a manic or mixed episode of bipolar I disorder with psychotic features (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria) and a baseline score =20 on the Young Mania Rating Scale (YMRS) were randomly assigned to quetiapine or VPA. Quetiapine was initiated at 150 mg/d and adjusted to a target dose ≤400 mg/d by day 4. VPA was initiated at 20 mg/kg per day and adjusted to achieve blood levels ≤70 mg/dL by day 4. Primary efficacy assessments, the YMRS and the Clinical Global Impressions Scale for Bipolar Disorder (CGI-BD), were administered at baseline and on days 2, 4, 7, and 14. Outcome data were evaluated with repeated-measures analysis of variance, with last observations carried forward for noncompleters. The percentage of responders (defined by ≤25% reduction in symptoms on each rating instrument) by group was evaluated by chi-squared analysis.

Results: The sample comprised 20 patients, aged 19 to 55 years; 11 were assigned to quetiapine, 9 to VPA. The only significant between-group difference in baseline characteristics was the percentage of patients with current or past substance use disorders, which was higher in the quetiapine group. Mean final doses were 656 mg/d for quetiapine and 1607 mg/d for VPA. Two patients from each group did not complete the study. Both groups showed significant and similar reductions in overall and manic symptoms, but only the quetiapine group improved significantly on the CGI-BD depression scale. Between-group differences in the percentage of responders were not significant. Both treatments were well tolerated. The most common adverse events were tremor (33% with VPA vs 0% with quetiapine), headache (22% vs 9%), sedation (0% vs 18%), and constipation (11% vs 18%).

Conclusion: These preliminary data suggest that quetiapine administered in escalating doses is as efficacious and well tolerated as VPA in treating manic episodes, and may be more efficacious in reducing depressive symptoms.

Source(s) of Funding: The research presented was supported by AstraZeneca Pharmaceuticals LP.

POSTER NO. 69

ASSESSING THE FUNCTIONAL STATUS OF BIPOLAR PATIENTS

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Objectives: Bipolar disorder, as well as some of the pharmacological agents used to treat it, often impairs patients' ability to function on a day-to-day basis. The goal of the present study was to either identify or develop a sensitive, psychometrically sound, patient-reported instrument to facilitate the identification of treatments effective in maximizing the functional status of bipolar patients.

Preliminary Research: A team of psychometricians conducted an extensive evaluation of available functional status instruments and presented the results to a panel of key opinion leaders, including three measurement experts and three clinicians. The group concluded that none of the existing measures was ideal, because they were either generic in nature or had not been validated within a bipolar population. Therefore, all parties agreed to collaborate on the development of a new bipolar-specific functional status instrument.

Methods: First, relevant constructs were identified through consultation with the key opinion leaders, literature review, and a series of individual in-depth interviews with bipolar patients. The team then worked collaboratively to create 50 items addressing each of the following domains: cognitive functioning, sleep, role functioning, emotional functioning, energy/vitality, social functioning, personal management, and sexual functioning. Finally, the draft questionnaire was tested and revised through two iterative sets of cognitive interviews with 19 additional patients in multiple locations.

Results: In general, the pretest participants deemed the set of constructs addressed in the questionnaire to be both comprehensive and representative of their daily functioning. They also reported that the final set of items was easy to comprehend and complete, noting that the 7-point Likert-type response scale seemed optimal - the points on the scale appeared to represent the full spectrum of answer choices, yet participants could easily distinguish between the options. Cognitive testing also resulted in the elimination of 17 items, which were either deemed inessential to the measurement of functional status, were applicable only to a subset of patients (e.g., family responsibilities), or were too similar in content to other items.

Conclusion: The resulting questionnaire addresses all constructs central to the functional status of patients with bipolar disorder with 33 items that are phrased to facilitate patient comprehension and completion. A multi-site, 600-patient validation study is currently underway to evaluate the psychometric properties of this instrument.

Source of Funding: AstraZeneca Pharmaceuticals LP

POSTER NO. 70

DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT STUDY OF MEXILETINE FOR MANIA OR HYPOMANIA

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Background: Mexiletine hydrochloride is an anticonvulsant with a similar mechanism of action to currently used mood stabilizers. Open-label data has suggested efficacy of mexiletine for treatment-resistant bipolar disorder. The purpose of this study was to identify whether mexiletine is efficacious and safe for the treatment of mania or hypomania.

Methods: A 3-week, randomized, double-blind, placebo-controlled, add-on study in bipolar disorder (BD) patients with current hypomania or mania. Patients remained on their baseline medications throughout the course of the study.

Results: Ten subjects (7 female, 3 male) outpatients were enrolled in the study. Six subjects with BD type I, and four subjects with BD type II. There was no significant difference in age (mean age = 46.9 years, SD = 9.4) or baseline YMRS score between the treatment groups. Mean change in YMRS score among subjects on mexiletine compared to placebo was -12.4 versus -9.6, respectively. Mexiletine was generally well tolerated, and there were no serious adverse events.

Conclusions: This pilot study suggests that mexiletine hydrochloride may be an efficacious treatment for some patients with bipolar disorder. Larger trials are required to confirm these results.

Sources of Funding: The Stanley Medical Research Institute; Physicians Services Incorporated Foundation

POSTER NO. 71

USE OF A NATURALISTIC DATABASE TO STUDY PATIENTS AND OUTCOMES IN BIPOLAR DISORDER WITH AND WITHOUT COMORBID SUBSTANCE USE

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Introduction: Studying clinical outcomes typically involves the execution of clinical trials to collect information. However, the longitudinal data repository of psychiatry patients at Duke Medical Center includes clinical and outcomes information, HIPAA compliant, from an actual treatment setting. In this retrospective study, outcomes of bipolar patients with and without comorbid substance abuse were studied.

Methods: The data repository, comprising 18,000 psychiatric patients' information and 110,000 qualified clinical visits, is compiled as a result of the use of the proprietary Clinical Research. The quality of the clinical data is maintained by defining a qualified clinical visit for each patient encounter, which includes: medications, psychiatric diagnosis, side effects, CPT billing codes, CGI, and allergies. CRIS is fully deployed throughout the continuum of care including emergency room, inpatient and outpatient services.

Of the patients in the data repository with a diagnosis of bipolar disease, patients who received any of the following treatments were included in this study: valproic acid or its derivatives; atypical antipsychotics; or mood stabilizers including lithium, carbamazepine, oxcarbazepine, lamotrigine, or topiramate.

Results: A total of 1750 patients with bipolar disease received at least one of the treatments listed. Of those, 495 were classified as valproate patients; 539 as atypical antipsychotics; 277, lithium; 187, lamotrigine; 102, carbamazepine; 97, topiramate; and 53, oxcarbazepine. Sixty-one percent were female.

A larger percentage of African Americans received atypical antipsychotics than did Caucasians or Others (42% vs. 28%, 28% respectively). Within each race group, roughly equivalent percentages received valproic acid (29%, 28% and 32% respectively).

Of patients between the ages of 13 and 64, 30% received atypical antipsychotics; of those patients either 12 or less or 65 and older, 37% received atypicals.

No differences were noted in the distribution of treatments received for the 1250 bipolar patients vs. 500 bipolar patients with comorbid substance abuse.

Within each of the two bipolar groups an estimate of treatment efficacy was explored by reviewing absolute differences in CGI-Severity and -Improvement scores, as well as the duration of intra-episode stability.

Our results generally depict a population with recurring symptomatology often on poly- pharmaceutical regimens with frequent alterations in treatment. An expected adverse effect of comorbid substance abuse on intra-episode stability and duration of stability was confirmed.

Summary: In a longitudinal, actual treatment setting, some variability within mood stabilizer treatments is noted for age and race. Further, in this observational setting, a general lack of stability for treated bipolar patients is noted, with a worsening among those treated bipolar patients with comorbid substance abuse.

Source of Funding: Abbott Laboratories

POSTER NO. 72

EXTENDED-RELEASE CARBAMAZEPINE FOR THE TREATMENT OF BIPOLAR DISORDER

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Objective/Background: Carbamazepine (CBZ) has long been considered a standard therapy for bipolar disorder. Extended-release formulations of carbamazepine were developed to decrease dosing frequency and to decrease plasma fluctuations associated with immediate-release formulations. A retrospective study was conducted to evaluate the effectiveness and safety of extended-release carbamazepine capsules (ERC-CBZ; SPD417) in the treatment of bipolar disorder in an outpatient setting.

Methods: A chart review of 180 adult and pediatric outpatients aged 7-55 with DSM-IV bipolar disorder and treated with ERC-CBZ was conducted (mean age 24.1 ± 12.8 years; 57% female; 57% bipolar I, 23% bipolar II, 20% bipolar NOS). Charts of subjects who received ERC-CBZ in a private practice setting (LDG, Red Oak Psychiatry Associates, Houston, TX) between October 1998 and August 2003 were reviewed. Treatment response was assessed with the Clinical Global Impressions-Improvement (CGI-I) scale (1 = very marked improvement; 2 = moderate improvement). Relapse was defined as a mood change that occurs four weeks after initiation of medication or the return of symptoms from the original episode.

Results: Forty-nine subjects (48%) taking ERC-CBZ had marked to moderate improvement (CGI-I score: 1, 27%; 2, 21%). No subjects experienced moderate to marked worsening. Forty-eight patients (27%) relapsed during ERC-CBZ treatment (mean time to relapse = 173 days). Mixed symptoms were the most common bipolar illness presentation. The mean ERC-CBZ dose was 646 mg/d and the mean serum concentration was 7.3 mcg/ml. Dizziness (8%) and nausea (8%) were the most frequently reported side effects.

Conclusion: Extended-release carbamazepine appears effective in the treatment of bipolar disorder and was well tolerated.

Source(s) of Funding: Shire, Newport, KY

POSTER NO. 73

ADJUNCTIVE ZIPRASIDONE IN BIPOLAR MANIA: LONG-TERM DATA

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Objective/Background: Antimanic agents may require 2 to 3 weeks for acute symptom control, making adjunctive antipsychotic therapy attractive. Because ziprasidone has shown rapid efficacy in acute mania, we investigated its use in bipolar patients receiving lithium.

Methods: Lithium-treated bipolar inpatients with Mania Rating Scale (MRS) score =14 were randomized to ziprasidone (80-160 mg/d) or placebo for 21 days. Lithium serum levels were maintained at 0.8-1.2 mEq/L. Between-group differences in rate of change and LS mean change were compared. A 104-week, open-label study (ziprasidone 40-160 mg/d) assessed mean endpoint changes from continuation baseline (LOCF).

Results: Day 4 rate of change was significant with ziprasidone (n=102) but not with placebo (n=103) for MRS, Clinical Global Impression-Severity (CGI-S), CGI-Improvement (CGI-I), Behavior and Ideation Subscale, and Hamilton Depression Rating Scale (Ham-D). Day 14 rate of change in MRS and CGI-S (the primary endpoints) was comparable, but mean changes with ziprasidone were significantly greater for variables of the Positive and Negative Syndrome Scale (PANSS) at Days 14 and 21. Improvement from continuation baseline (n=89) stabilized at Weeks 4-12 for MRS, at Weeks 12-28 for CGI-S, and after Week 52 for PANSS Positive scores. MRS and PANSS Positive improvements were sustained to endpoint; PANSS Total improvement was sustained until Week 28, with fluctuations thereafter. The most common side effects were somnolence and extrapyramidal symptoms (usually mild or moderate). There was no change in median weight, and only one case of glucose 1.5 x ULN. No subject had QTc interval =480 msec despite concomitant treatment with lithium.

Conclusion: Ziprasidone plus lithium effected significantly greater Day 4 rate of change in mania-related psychopathology, suggesting more rapid efficacy than with lithium alone. Long-term improvements were sustained, with good tolerability.

Source(s) of Funding: Supported by funding from Pfizer, Inc.

POSTER NO. 74

QUETIAPINE IN THE TREATMENT OF DEPRESSIVE SYMPTOMS IN BIPOLAR MANIA

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Objective/Background: Evaluate the effect of quetiapine on depressive symptoms in patients from double-blind studies of bipolar mania.

Methods: Depressive symptoms were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) in patients with bipolar I disorder (manic episode, DSM IV) who received quetiapine alone (up to 800 mg/day; 12 weeks) or combined with lithium (0.7-1.0 mEq/L) or divalproex (50-100 µg/mL) (3 or 6 weeks). Treatment-emergent depression, defined a priori as a MADRS score =18 with an increase from baseline of =4 at any two consecutive assessments or at the last observation, was also monitored.

Results: In a combined analysis, the proportion of patients with treatment-emergent depression was low and similar in 2 monotherapy (quetiapine 4.3%, placebo 8.6%) and 2 combination therapy (quetiapine 10.7%, placebo 9.8%) studies. MADRS scores were reduced significantly with quetiapine monotherapy versus placebo at Day 21 (-2.44 vs -0.78; P<0.001) and further at Day 84 (-2.61 versus 0.06; P<0.001). No significant difference was observed between groups in change from baseline in MADRS scores with combination therapy.

Conclusion: Quetiapine as monotherapy and in combination with lithium/divalproex is not associated with emergent depression. Quetiapine treatment may improve depressive symptoms in patients with bipolar disorder.

Source(s) of Funding: This research was supported by AstraZeneca.

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POSTER NO. 75

DIVALPROEX AS ADJUNCTIVE THERAPY TO ATYPICAL ANTIPSYCHOTIC

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Objective/Background: Evaluation of the efficacy of divalproex in reducing residual mood symptoms in patients (DSM-IV diagnoses of schizophrenia, schizoaffective disorder, bipolar depression, and major depressive disorder), and independence from baseline severity of illness (SOI) scores and type of atypical antipsychotic.

Methods: 49 patients stabilized on atypical antipsychotics and divided into 3 illness groups by SOI: Group 1=mild/moderate, Group 2=marked, Group 3=severely/most extreme. Antipsychotics used were clozapine (n=11), risperidone (n=21), olanzapine (n=10), and quetiapine (n=7). Divalproex delayed release was initiatied at 20 mg/kg and adjusted by blood level (mean level=84 mcg/mL)]. BPRS, Clinical Global Impressions (CGI-S) and Patient Target Complaints (PTC) were assessed at baseline and 4 weeks posttreatment .

Results: Analysis indicated adjunctive divalproex with atypical antipsychotic medications significantly improved residual depression ($p<.0001$) and irritability symptoms ($p<.0001$) independent of antipsychotic regimen ($p=.4587$) or inpatient/outpatient status ($p=.0721$). 71% of patients had CGI-S scores of "much improved" or better. Significant improvements in BPRS ([P=.004] Group 1= -3.7; Group 2= -7.52, Group 3= -10.88) and PTC ([P=.003] -2.5, -4.64, and -6.4, respectively) scores were also seen.

Conclusion: Adjunctive divalproex significantly improved residual irritability and depression symptoms in patients stabilized on atypical antipsychotics and appeared to produce greater improvement in patients with higher SOI scores.

Source(s) of Funding: Abbott Laboratories

POSTER NO. 76

RISPERIDONE VERSUS OLANZAPINE AS ADJUNCTIVE THERAPY IN THE TREATMENT OF PATIENTS WITH BIPOLAR DISORDER WHO ARE RECEIVING A PRIMARY THYMOLEPTIC AGENT

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Objective/Background: Recently, the atypical antipsychotics have been shown to be efficacious in the treatment of bipolar disorder.

Methods: A study was conducted to evaluate the comparative efficacy of olanzapine versus risperidone in the treatment of bipolar patients. Patients in an acute manic or mixed bipolar episode were randomly assigned to receive adjunctive olanzapine or adjunctive risperidone in an 8-week, double-blind study. Patients were assessed at baseline and weeks 1, 2, 4 and 8. Clinical measures included the YMRS, BPRS, and HAM-D. Twenty patients were randomized to olanzapine versus 16 who were randomized to risperidone.

Results: Results indicated a more rapid reduction in clinical symptoms for patients treated with risperidone than for patients treated with olanzapine, as measured by the YMRS (significantly greater reduction in symptoms for patients treated with risperidone versus olanzapine at week 2; $p<.05$) and BPRS (significantly greater reduction in symptoms for patients treated with risperidone versus olanzapine at weeks 1, 4 and 8; $p<.05$). However, there were no significant differences between groups on clinical measures at study endpoint.

Conclusion: There were significant between-group differences on weight at study endpoint. Patients treated with olanzapine gained significantly more weight than patients treated with risperidone.

Source(s) of Funding: Janssen Pharmaceutica Products, L.P.

POSTER NO. 77

PAROXETINE AND SUICIDALITY IN A HIGH-RISK POPULATION

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Objective/Background: In mid-2003 the US Food and Drug Administration (FDA) notified health care providers that use of paroxetine (Paxil, Seroxat) in adolescents 18 years-old or younger with major depressive disorder is associated with a three-fold increased risk of suicidal ideation and attempts. In December, 2003, the UK Department of Health has issued a similar warning, extended to include most serotonin reuptake-inhibitor (SRI) antidepressants.The advisories have begun to change clinical practice, although the actual data are not yet available to the field. It is therefore important to investigate promptly other datasets that might extend or limit the degree of risk of suicidality in individuals treated with paroxetine. The dataset from the STEP-BD network provides a novel opportunity to investigate the association of paroxetine and suicidality prospectively under general clinical practice conditions in a high-risk population.

Methods: The first 1,000 participants who completed at least 1 year of prospective follow-up in STEP-BD were followed with structured assessments under naturalistic conditions. Episode status according to DSM-IV, current medications, and suicidality was determined using the structured Clinical Monitoring Form (CMF), which was administered at each clinic visit.

Results: Three analyses were conducted using Fisher's exact test. Rates of suicidality were not increased with paroxetine treatment in: (a) participants >21 years old in a major depressive episode assessed cross-sectionally, (b) participants >21 years old with a prospectively observed new-onset depressive episode, or (c) participants 15-20 years old followed prospectively for 1 year.

Conclusion: It is reassuring for clinical practice that no association of suicidality with paroxetine treatment was found in this large bipolar disorder sample, who represent such a high-risk population. We cannot exclude the possibility that adolescents, or individuals with unipolar depression, represent a higher level of risk than those in this sample. Nonetheless, it appears from this large dataset that increased suicidal risk with paroxetine does not extend across mood disorders and across the life cycle.

Source(s) of Funding: This work was supported by the NIMH Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), Contract N01MH80001.

POSTER NO. 78

A PROSPECTIVE OPEN LABEL STUDY OF ZIPRASIDONE AUGMENTATION FOR BIPOLAR I DEPRESSION

This abstract may be found in the program and poster addendum.

POSTER NO. 79

COMPARISON OF OLANZAPINE AND LITHIUM TREATMENT GROUPS BASED ON LITHIUM BLOOD LEVELS: A 52-WEEK BIPOLAR RELAPSE PREVENTION STUDY

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Objective/Background: Lithium is considered a standard treatment for prophylaxis in bipolar disorder. Appropriate blood lithium levels for maintenance have been reported to be between 0.8 and 1.0 mmol/L. Efficacy of olanzapine versus lithium subgroups, based on blood levels, has previously not been reported.

Methods: This 52-week, randomized, parallel, double-blind study compared bipolar relapse on flexibly-dosed lithium or olanzapine. For this analysis, we defined two post-hoc lithium subgroups. Lower level group (LLG) comprising subjects with mean lithium levels <0.8 mEq/L and Higher level group (HLG) comprising subjects with mean lithium levels >0.8 mEq/L.

Results: The olanzapine treatment group had a greater time to relapse into mania or depression (YMRS total score >15 or/and HAMD-21 total score >15 or/and hospitalization for mania or depression) compared to the HLG (p=.014) but not to the LLG. The olanzapine treatment group had lower rates of manic relapse based on hospitalization for relapse and/or symptomatic rating scale criteria than both lithium treatment groups (olanzapine 14.7% vs. LLG 30.5%; p=.002 and HLG 32.9%; p<.001).

Conclusion: The olanzapine-treated patients had statistically significant lower rates of manic relapse than lithium treated patients, irrespective of lithium level.

Source(s) of Funding: Eli Lilly and Company

POSTER NO. 80

RILUZOLE: AN INVESTIGATION OF THE ANTIDEPRESSANT EFFICACY OF AN ANTIGLUTAMATERGIC AGENT WITH NEUROTROPHIC PROPERTIES IN BIPOLAR DEPRESSION

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Background: Since a significant percentage of depressed patients do not respond adequately to existing monoaminergic-based treatments, there is a clear need to develop improved therapeutics with novel mechanisms of action. Preclinical evidence indicates that chronic antidepressant administration causes adaptive changes in radioligand binding to NMDA receptors in mice. Furthermore, NMDA antagonists (MK-801 and AP-7) have antidepressant effects in animal models of depression. Clinical data in support of a glutamatergic strategy include the antidepressant effect of lamotrigine in bipolar depression and ketamine. Recently, our group reported the antidepressant properties of riluzole, another glutamatergic modulator in patients with treatment-resistant unipolar depression. Together, the data suggest that medications which directly reduce glutamatergic neurotransmission may represent a novel class of antidepressants. We are therefore investigating the antidepressant effects of riluzole in patients with bipolar depression.

Method: This is an 8-week add-on study examining the efficacy and safety of riluzole, a glutamatergic modulator in combination with lithium (therapeutic levels) in acutely depressed I and II patients ages 18 and older. Patients who failed to respond to at least 4 weeks of lithium monotherapy and had a Montgomery-Asberg Depression Rating Scale (MADRS) score of =20, received open treatment with riluzole (50-200 mg/day) in conjunction with stable therapeutic doses of lithium after a 1-week placebo lead in period. Efficacy is being assessed by mean changes in the MADRS from baseline to the end of the active phase.

Results: Ten subjects have been entered into the trial and recruitment is still ongoing. Remission (MADRS =10 at endpoint) has been observed in 40% of the patients.

Conclusions: These preliminary results suggest that riluzole may indeed have antidepressant efficacy in subjects with treatment-resistant bipolar depression. Results including a larger sample will be presented at the meeting.

Source(s) of Funding: National Institute of Mental Health.

POSTER NO. 81

CARNITINE LEVELS IN PSYCHIATRIC PATIENTS TREATED CHRONICALLY WITH VALPROIC ACID

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Objective/Background: The amino acid derivative carnitine is present in most human tissues where it facilitates the transport of long-chain fatty acids across the mitochondria for beta-oxidation, and the esterification of potentially toxic acyl-CoA metabolites. Studies have shown a significant decrease in carnitine concentrations in patients treated with valproic acid (VPA). Despite its relevance in other areas of medicine, no studies have been conducted to date to determine the role of VPA in carnitine depletion, or its effect in hepatic or pancreatic toxicity in psychiatric patients.

Methods: Thirty psychiatric subjects receiving VPA for at least 6-months were invited to participate. They were excluded if they had pre-existing liver disorder or pancreatitis, metabolic defects known to affect carnitine function, or were noncompliant with VPA. Serum free-, total-, and acyl-carnitine, VPA levels, and liver function tests were obtained. Pearson's correlations were conducted between VPA levels and the free- total-, and acyl-carnitine, VPA and acyl/free-carnitine ratio, as well as between VPA, carnitines, and liver function tests.

Results: Serum levels of free-carnitine were (mean ± standard deviation) 25.36 ± 7.27, acyl-carnitine 8.24 ± 2.23, and total-carnitine 33.6 ± 8.23 (considerably lower than reported normal range). The ratio of acyl/free carnitine was increased as previously reported in non-psychiatric VPA treated subjects. VPA levels had a mean of 75.9 ± 27.99, and duration of treatment was 30.83 ± 33.8 months. There was a significant negative correlation between VPA levels and carnitine (Pearson's R= -.320, one-tailed p= .048, two-tailed p=.096), VPA levels and ammonia (Pearson's R= .285, one tailed p= .063, two-tailed p=.14), very importantly VPA levels and acyl/free carnitine ratio(Pearson's R= .557, one-tailed p= .016, two-tailed p=.008). VPA levels correlated also several liver function indicators, and carnitine levels correlated with amylase.

Conclusion: Although limited by a cross sectional design without control comparison, the findings suggest that patients with various psychiatric conditions treated with polypharmacy that includes VPA, may have lower serum carnitine levels than expected for healthy controls.

Source(s) of Funding: Sigma Tau

POSTER NO. 82

DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF QUETIAPINE IN BIPOLAR DEPRESSION

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Objective: Evaluate efficacy and tolerability of quetiapine monotherapy for major depressive episodes in patients with bipolar disorder.

Method: 539 patients (358 bipolar I, 181 bipolar II depression) randomized to 8 weeks double-blind treatment with quetiapine (fixed dose 300 or 600 mg/d) or placebo. Primary endpoint: change from baseline to endpoint in Montgomery-Asberg Depression Rating Scale (MADRS) total score.

Results: Patients taking quetiapine 300 and 600 mg/d had a significantly ($P<0.001$) greater improvement in mean MADRS and HAMD scores vs placebo at every assessment starting with the first evaluation (Day 8) and sustained through endpoint (Week 8) (MADRS: -16.7 and -16.4 vs -10.2) (HAMD: -13.8 and -13.4 vs -8.5). Significantly ($P<0.05$) more quetiapine patients (both doses) vs placebo were considered responders ($\geq$50% decrease from baseline MADRS score) from week 2 through the end of the study. Treatment-emergent mania did not differ between quetiapine and placebo (3% vs 4%). Common quetiapine adverse events ($\geq$10% and $\geq$2x placebo rate) were dry mouth (43%), sedation (31%), somnolence (26%), dizziness (20%), and constipation (11%).

Conclusions: Quetiapine monotherapy (300 or 600 mg/d) is significantly more effective than placebo and well tolerated for the treatment of depressive episodes in patients with bipolar disorder.

Source(s) of funding: This research was supported by AstraZeneca.

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POSTER NO. 83

CARE SATISFACTION, HOPE, AND LIFE FUNCTIONING AMONG ADULTS WITH BIPOLAR DISORDER: DATA FROM THE FIRST 1,000 STEP-BD PARTICIPANTS

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Objective/Background: The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) is designed to evaluate the longitudinal outcome of patients with bipolar disorder. The STEP-BD treatment model encourages patients and their providers to combine their efforts in deciding the best pharmacological and psychosocial treatment options available (Sachs,1996). Whereas ineffective treatment alliances may exacerbate negative expectations of future outcomes, hopelessness, loss of motivation, and demoralization (Beck, Wiessman, Lester et al, 1974; Hill, Gallagher, Thompson et al, 1988, Clarke, Kissane, 2002), a collaborative, patient-centered treatment relationship created through education and support is expected to enhance patients' self-efficacy, hope, and life functioning. This prospective study examined the longitudinal relationships between the first 1,000 STEP-BD patients' satisfaction with care, levels of hope, and life functioning.

Methods: The study used scores from the Care Satisfaction Questionnaire, Beck Hopelessness Scale, Range of Impaired Functioning Tool, Young Mania Rating Scale, and Montgomery-Åsberg Depression Rating Scale at five time points during a one-year interval. Analyses were performed in two phases. Phase I analyses explored the psychometric properties of all instruments. Phase II analyses tested mediational pathways between care satisfaction, hope, life functioning, depression, and mania using mixed effects (random and fixed) regression models.

Results: Increases in care satisfaction were associated with decreased hopelessness ($F(1, 79) = 9.22$, $p < .01$), but not related to symptoms of depression or mania. Similarly, decreased hopelessness was associated with better life functioning ($F(1, 109) = 8.80$, $p < .01$), but not related to symptoms of depression or mania. Depression was also strongly associated with poorer life functioning ($F(1, 93) = 262.37$, $p < .0001$).

Conclusion: This study provided support for the hypothesized mediational pathway between care satisfaction, hopelessness, and life functioning. Findings suggest that if an ultimate treatment objective is enhanced life functioning, providing care that maximizes patient hope in addition to decreasing symptoms may be important. By so doing, patients might overcome the learned helplessness/ hopelessness that often accompany cyclical illness and build a realistic illness management strategy. Treatment models might achieve this by assisting patients with bipolar disorder to build the professional, social, and familial supports that are protective factors against depression (Miklowitz, Goldstein, Nuechterlein et al, 1988) and training patients to cope with psychosocial stress agents that often exacerbate bipolar illness (Johnson & Roberts, 1995; Johnson & Miller, 1997; Miklowitz and Frank, 1999).

Source(s) of Funding: This project has been funded in part with Federal funds from the National Institute of Mental Health (NIMH), National Institutes of Health, under Contract N01MH80001.

POSTER NO. 84

PREVIOUS LITHIUM TREATMENT AS A PREDICTOR OF RESPONSE TO SUBSEQUENT MOOD STABILIZER THERAPY

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Objective/Background: Lithium continues to be the reference standard among mood stabilizers. Two large maintenance studies have been completed studying both lithium and the anticonvulsant mood stabilizer, lamotrigine, enrolling both recently depressed (GW605) or manic/hypomanic/mixed (GW606) outpatients. This analysis examined whether previous lithium experience predicted subsequent response to lithium or lamotrigine in these studies.

Methods: 588 currently or recently symptomatic bipolar I patients (DSM-IV) were randomized to 18 months of double-blind monotherapy with lamotrigine (100-400mg/day), lithium (0.8-1.1mEq) or placebo. Efficacy outcomes (time from randomization until intervention for an emerging manic or depressive episode) were examined according to previous lithium history.

Results: The study population included 336 (62%) patients with previous lithium treatment, of whom 237 (71%) reported clinical response. Among previous lithium responders, median survival time to relapse was prolonged for both subsequent lithium (166 days) and lamotrigine (156 days) treatment compared with placebo (42 days). For the smaller subset of patients not previously responding to lithium, neither subsequent lithium (123 days) nor lamotrigine (91 days) significantly prolonged survival compared with placebo (93 days).

Conclusion: Previous positive response to lithium appears to be predictive of subsequent response to lithium or lamotrigine.

Source(s) of Funding: Funding provided by GlaxoSmithKline

POSTER NO. 85

CHARACTERISTICS OF PATIENTS TREATED WITH GABAPENTIN REFERRED TO A BIPOLAR SPECIALTY CLINIC

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Objective/Background: Gabapentin remains widely prescribed to patients with bipolar disorder despite randomized clinical trials suggesting lack of efficacy. The characteristics of patients with bipolar disorder prescribed gabapentin were compared to bipolar patients not prescribed gabapentin. We hypothesized that patients taking gabapentin were prescribed this anticonvulsant because they had more comorbid anxiety disorders.

Methods: The charts of 30 patients prescribed gabapentin prior to clinic entry were compared to 30 age- and sex-matched patients not prescribed gabapentin prior to clinic entry. All subjects were evaluated after the publication of data suggesting that gabapentin is ineffective for bipolar disorder. Baseline evaluation included demographics, concurrent medications, current depressive and manic symptoms, lifetime depressive and manic/hypomanic episodes, prior suicide attempts and violence, age of onset, and comorbid anxiety, substance use, and personality disorders.

Results: There was significant difference between groups on the number of medications, with the gabapentin group taking more medications. ($p = .01$). Using t-tests and chi-square analyses, no significant differences were found for any other variables between groups.

Conclusion: The hypothesis that patients prescribed gabapentin had a higher rate of comorbid anxiety disorders was not supported. Gabapentin appears to be used as a mood stabilizer despite the lack of evidence supporting this use of the drug. This suggests that there is a lag between research and clinical practice.

Source(s) of Funding: Stanley Foundation

POSTER NO. 86

USING MOOD STATE TO PREDICT POLARITY OF RELAPSE IN BIPOLAR MAINTENANCE STUDIES

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Objective/Background: Few controlled maintenance trials in bipolar disorder assess patients whose index episode (IE) is depression. Yet, IE may play an important role in predicting polarity of subsequent episodes and therefore, response to treatment.

The objective of this research was to examine the relationship of polarity of IE with polarity of subsequent mood episodes.

Methods: A systematic literature search was conducted using MEDLINE and supplemented with data from two recent 18-month maintenance trials of lithium and lamotrigine (GW605/606). The ratio of polarity of IE to subsequent episode (depressed, manic) was examined for patients treated with placebo (natural course of the illness).

Results: Prien et al (1973) showed that patients were twice as likely to relapse to the IE as opposed to a mood episode of opposite polarity. More recent data showed that patients with IE of depression had a 2.5:1 ratio of subsequent depressive to manic episodes whereas patients with IE of mania had a 1.3:1 ratio of subsequent manic to depressive episodes.

Conclusion: Polarity of IE appears to be associated with a reoccurrence of a subsequent mood episode of the same polarity. To fully examine efficacy of maintenance treatments for bipolar disorder, clinical trials should enroll patients with both depressive and manic IE.

Source(s) of Funding: Research funded by GlaxoSmithKline

POSTER NO. 87

AN INTERACTIVE COMPUTER INTERVIEW FOR MANIA TO ENHANCE HUMAN RATER PERFORMANCE

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Objective/Background: Reliance on rating scales administered by human raters likely contributes to the high failure rate of multi-center randomized clinical trials in psychiatry. Even a modest reduction in the variance of clinical ratings can increase statistical power and reduce sample size requirements. We developed an automated system that can monitor the quality of clinical rating scales administered by humans by conducting an independent evaluation. The Interactive Computer Interview for Mania (ICI-M) is a self-rated, computerized interview that utilizes an algorithm of probes designed to assign symptom severity ratings based upon the Young Mania Rating Scale (YMRS). The goal of the ICI-M is not to replace the human rater, but to enhance the sensitivity and consistency among human raters by creating "check" on the human rater. The study objective was to establish the feasibility, reliability, and validity of the ICI-M.

Methods: Eligible subjects met DSM-IV criteria for Bipolar disorder and provided written consent. In counterbalanced order, subjects participated in a videotaped YMRS interview with an experienced human rater (LR) and the ICI-M. Participants also completed a modified version of the Client Satisfaction Questionnaire (CSQ). A committee of experienced raters, blind to the LR and ICI scores, reviewed the videotape to assign a consensus rating (CR) for each YMRS item.

Results: 100 Bipolar I or II subjects participated (age range 19-71 yrs, Female 60%, Non-Caucasian 17%). Intraclass correlation coefficients (ICCs) were .91 between the ICI-M and CR and .97 between the LR and CR, providing empirical support for the validity of each approach. Coefficient alphas indicated comparable internal consistency reliability: ICI-M=.82, LR =.83, and CR=.84. Mean scores of each method were ICI-M=24.7, LR =21.3, CR=20.9. The ICI-M was significantly more sensitive than LR ($p<.001$) and CR ($p<.001$), and resulted in significantly higher ratings than CR on mood, speech, psychotic content, and disruptive-aggressive behavior. The CSQ showed no significant differences between ICI-M and LR regarding comfort level, willingness to participate again, or ability to understand the questions.

Conclusion: The ICI-M is a well-accepted, reliable, and valid method for assessing manic symptoms. The concordance between ICI-M and CR was substantially stronger than that typically found between two human raters. The ICI-M is a tool with adequate sensitivity to elicit symptoms and rate severity and is recommended to monitor and improve rater performance, not as a replacement to a human rater.

Source(s) of Funding: NIMH Grant 1 R43 MH65796-01A1, Noreen Reilly-Harrington, Ph.D, Principal Investigator

POSTER NO. 88
PRAMIPEXOLE FOR BIPOLAR II DEPRESSION

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Objective/Background: The original serotonergic and noradrenergic hypotheses do not fully account for the neurobiology of depression or mechanism of action of effective antidepressants. Research implicates a deficiency of dopaminergic system in the pathophysiology of depression. The current study was undertaken as a proof of the concept that dopamine agonists will be effective in patients with bipolar II depression.

Methods: In a double-blind, placebo-controlled study, 21 patients with DSM-IV bipolar II disorder, depressive phase on therapeutic levels of lithium or valproate, were randomly assigned to treatment with pramipexole (N=10) or placebo (N=11) for 6 weeks. Primary efficacy was assessed by the Montgomery-Asberg Depression rating scale (MADRS).

Results: All subjects except for one in each group completed the study. The ANOVA for total MADRS scores showed a significant treatment effect. A therapeutic response (>50% decrease in MADRS from baseline) occurred in 60% of patients taking pramipexole and 9% taking placebo (p=.02). Mean percentages in improvement from baseline to endpoint MADRS depression ratings were greater with pramipexole (47%) than placebo (12%) (p<.007). One subject on pramipexole and two on placebo developed hypomanic symptoms.

Conclusion: The dopamine agonist pramipexole was found to have significant antidepressant effects in patients with bipolar II depression. Large-scale randomized double-blind placebo controlled trials are indicated to determine that pramipexole will be a clinically useful treatment.

Source(s) of Funding: NIMH Intramural

POSTER NO. 89

SAFETY AND TOLERABILITY OF QUETIAPINE IN BIPOLAR MANIA

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Objective: Evaluate the safety and tolerability of quetiapine in the treatment of mania.

Methods: Adverse events (AE), Simpson Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and prolactin levels were monitored in patients with bipolar I disorder (manic episode, DSM IV) randomized to double-blind, placebo-controlled treatment with quetiapine (up to 800 mg/day) monotherapy (2 studies; 12 weeks) or in combination with lithium (0.7-1.0 mEq/L) or divalproex (50-100 µg/mL) (2 studies; 3 or 6 weeks).

Results: Most AEs were mild to moderate and discontinuations due to AEs were no different from placebo. Mean weight change (LOCF) at end of treatment for quetiapine versus placebo was +1.8 kg vs -0.15 kg (monotherapy) and +1.58 kg vs +0.17 kg (combination therapy). No patients withdrew due to weight gain. The incidence of extrapyramidal symptoms (including akathisia) in quetiapine-treated patients was no different from placebo. The mean change from baseline to end of treatment in SAS and BARS scores was not statistically significantly different between groups. The effect of quetiapine on prolactin levels was no different from placebo across the dose range. Quetiapine was not associated with treatment-emergent depression.

Conclusions: Quetiapine is well tolerated in the treatment of mania associated with bipolar disorder.

Source(s) of funding: This research was supported by AstraZeneca.

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POSTER NO. 90

RELATION OF FUNDING-SOURCE, METHODOLOGICAL QUALITY AND STUDY-OUTCOME IN BIPOLAR DISORDER DRUGS REPORTS

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Background: Since high quality of clinical research and its reporting is critical for progress in psychiatry and for rational practice, the Clinical Knowledge and Research Methodology Audit (ClinKARMA) project is systematically evaluating recent research reports in leading psychiatric journals. We now report preliminary findings pertinent to relations among funding-source, study-outcome and methodological quality of research papers on pharmacotherapy for bipolar disorder.

Methods: A random sample of drug treatment studies (1998-2002) was identified by MEDLINE and PsycINFO searches in 5 psychiatric journals with the highest Impact-Factors for 2001 as assessed by the Institute for Scientific Information. Funding sources and study outcome were assessed as reported in print; methodological quality evaluated according to study design (scored at 5 levels-of-evidence), conclusions based on p-values (i.e. a confounded measure), assessment of precision (confidence-intervals or power-analysis), drop-out rates in prospective studies, citation of the literature to support research design and analytical methods.

Results: In a representative sample of 22 original articles (sampling fraction =0.19), 7/7 sponsored by pharmaceutical corporations reported results favorable to sponsors' products vs. 7/15 favorable results with a novel treatment in studies without such funding (RR 2.14; 95%CI 1.25-3.68). 2/7 vs. 3/15 had a randomized design (1.43; 0.30-6.72). Among 13 prospective studies, 3/6 vs. 6/7 had a drop-out rate =40% (0.58; 0.25-1.37). 2/7 vs. 5/15 had references about design or statistical methods employed (0.86; 0.22-3.38). Only 3 studies addressed precision, all not pharmaceutically funded, while almost every report based conclusions on p-values.

Conclusion: Pharmaceutically funded studies tend to have a randomized design and lower drop-out rates but seem less likely to address precision. There is a clear association between pharmaceutical sponsoring and the publishing of results favorable to experimental drugs. Possible explanations include a more careful selection by the industry of which studies get funded, lack of an appropriate comparator or dosage in pharmaceutically-sponsored trials, and publication bias: negative industry-sponsored research could be less likely to be published compared to negative non-industry sponsored studies.

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POSTER NO. 91

WORK LOSS ASSOCIATED WITH BIPOLAR DISORDER

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Objective: To assess indirect costs of work loss associated with bipolar disorder and major (unipolar) depression.

Method: From MEDSTAT's employer-based MarketScan© database for 2000, workers (mean age 42 ± 9) with a primary ICD9-CM diagnosis of bipolar disorder (N=740), major depression (N=6,314), and one-to-one matched controls with no psychiatric diagnosis were identified. Work loss parameters were absence hours and payments for short-term disability and worker compensation.

Results: Mean annual absence hours were 55 (± 49) for the bipolar group vs 21 (± 27) for controls (P=0.009), and 53 (± 154) for the unipolar depression group vs 24 (± 48) for controls (P<0.0001). Mean short-term disability payments were $1,231 (± 3,424) for the bipolar group vs $131 (± 967) for controls (P<0.0001), and $741 (± 2,873) for the unipolar depression group vs $178 (± 1,309) for controls (P<0.0001). Mean worker compensation payments were $554 (± 4,231) for the bipolar group vs $228 (± 2,289) for controls (P=0.15), and $518 (± 4,814) for the unipolar depression group vs $220 (± 2,449) for controls (P=0.0001).

Conclusions: Bipolar disorder and major (unipolar) depression significantly increased work loss. Patients with bipolar disorder may exhaust their sick leave and go onto short-term disability more frequently than those with unipolar depression.

Source(s) of funding: This research was supported by AstraZeneca.

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POSTER NO. 92

AN OPEN LABEL STUDY OF LAMOTRIGINE IN ADOLESCENTS WITH BIPOLAR MOOD DISORDER

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Objective/Background: To evaluate the safety and efficacy of lamotrigine in the treatment of adolescent Bipolar I disorder (BD I), most recent episode depressed or mixed state.

Methods: This was a single center, outpatient, 12-week open-label study in adolescents (ages 13-17) diagnosed with BD I, depressed or mixed. Twenty-three patients entered the trial and thirteen completed 12 weeks of therapy. Children's Depression Scale-Revised (CDRS-R), Young Mania Rating Scale (YMRS), Clinical Global Impression-Severity (CGI-S) were outcome measures.

Results: Baseline mean scores were: CGI-S =4, CDRS-R= 73, and YMRS = 20 and at 12 weeks, scores were 1, 40 and 6, respectively. Mean starting dose of lamotrigine was 25 mg a day and at week twelve mean dose was 241 mg daily. Three subjects terminated early due to non-compliance, five were lost to follow-up, and two discontinued for suicidal ideation requiring hospitalization. No subjects discontinued for adverse events related to the study drug.

Conclusion: Lamotrigine appeared to be safe and efficacious in this population. Controlled studies are necessary to further evaluate the safety and efficacy of lamotrigine in this population.

Source(s) of Funding: GlaxoSmithKline

POSTER NO. 93

A PHARMACOKINETIC INTERACTION STUDY OF LAMOTRIGINE AND OLANZAPINE

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Objective/Background: Co-therapy with antipsychotics and antiepileptics is becoming increasingly common in bipolar disorder. The objective of this research was to examine the pharmacokinetic interactions of olanzapine (OLZ) added to lamotrigine (LTG) in healthy volunteers.

Methods: 52 non-smoking males (age 18-55 years) were randomized to LTG (titrated to 200mg/day) or placebo (PBO). OLZ (titrated to 15mg) or PBO were added on days 43-56 resulting in three parallel cohorts receiving the combination of LTG+OLZ (n=16), LTG+PBO (n=12) or OLZ+PBO (n=18) for 2 weeks. Serum blood levels, adverse events (AEs), and blood chemistry were examined. Pharmacokinetic profiles were obtained at steady state.

Results: LTG AUC (0-24) and Cmax were, on average, 24% and 20% lower with LTG+OLZ compared with LTG+PBO, respectively. OLZ AUC(0-24) and Cmax were comparable with OLZ+LTG and OLZ monotherapy. AEs were similar with LTG+OLZ and OLZ+PBO; fewer AEs were reported with LTG+PBO. The most common AEs were transaminase elevations, fatigue, and dizziness. Transaminase elevations and dizziness were reported at similar frequencies with LTG+OLZ and OLZ+PBO, but not with LTG+PBO.

Conclusion: The combination of OLZ and LTG was well-tolerated, with the type, frequency, and severity of adverse events similar to olanzapine monotherapy. These results support co-administration in patients who may benefit from combination therapy.

Source(s) of Funding: Funding provided by GlaxoSmithKline

POSTER NO. 94

LONG-TERM COGNITIVE IMPROVEMENT: ZIPRASIDONE VERSUS OLANZAPINE

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Background: It is unclear whether long-term treatment with atypical antipsychotics yields continuing improvement in cognitive function. We compared olanzapine and ziprasidone treatment of cognitive impairments in a double-blind 6-month extension of a 6-week randomized, clinical trial.

Methods: Patients entered the 6-week study naïve to both medications and could enter the extension if they had CGI-I =2 or =20% improvement in PANSS Total during the core study. A cognitive battery measured verbal learning, executive functioning, visuomotor speed, verbal fluency, and vigilance.

Results: In both ziprasidone (n=62) and olanzapine (n=71) groups, substantial cognitive improvements occurred from baseline to endpoint of the extension. Improvements (presented in effect size units for ziprasidone, but not significantly different between medications) in verbal learning were d=.97 and in delayed recall were d=1.07. Executive functioning also improved, with d=.66 for WCST errors. Trail making test part A improved by d=.60 and part B by d=.50. These improvements were significant (p<.01) and were generally uncorrelated with changes in PANSS or ESRS.

Conclusions: Long-term treatment of patients with early response to ziprasidone or olanzapine is associated with incremental cognitive gains that are at least twice that observed in short-term trials. Thus, cognitive benefits of atypicals may increase over time.

Source of Funding: Supported by funding from Pfizer Inc.

POSTER NO. 95

PHENOMENOLOGY OF RAPID CYCLING BIPOLAR DISORDER: DATA FROM THE FIRST 500 PARTICIPANTS IN THE SYSTEMATIC TREATMENT ENHANCEMENT PROGRAM FOR BIPOLAR DISORDER

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Objective: To compare demographic and phenomenological variables between rapid cycling bipolar patients and non-rapid cycling bipolar patients as a function of bipolar I versus bipolar II status.

Method: We examined demographic, historical and symptomatic features of rapid cycling and non-rapid cycling patients in a cross-sectional sample of the first 500 patients with bipolar I or bipolar II disorder enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). STEP-BD is a multi-center NIMH-funded project designed to evaluate the longitudinal outcome of patients with bipolar disorder.

Results: Rapid cycling bipolar disorder occurred in 20% of the sample. Rapid cycling patients were more likely to be female, although the effect was significantly more pronounced in bipolar I patients than bipolar II patients. In addition, rapid cycling bipolar patients experienced a younger age of onset of their illness, were more often depressed at study entry, and had poorer global functioning in the year prior to study entry than non-rapid cycling patients. Rapid cycling patients also experienced a significantly greater number of depressive and hypomanic/manic episodes in the prior year. A lifetime history of psychosis did not distinguish between rapid and non-rapid cycling patients, although bipolar I patients were more likely to have experienced psychosis than bipolar II patients.

Conclusions: Patients with rapid cycling bipolar disorder demonstrate a greater severity of illness than non-rapid cycling patients on a number of clinical measures. This study highlights the need to refine treatments for rapid cycling to reduce the overall morbidity and mortality of patients with this illness course modifier.

POSTER NO. 96

ZIPRASIDONE IN PEDIATRIC PATIENTS: EFFICACY AND TOLERABILITY

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Objective: To determine ziprasidone's efficacy and safety in pediatric patients requiring antipsychotic therapy for a variety of psychiatric disorders.

Methods: We retrospectively reviewed outpatient records for children <18 years started on ziprasidone and having outcomes data. Extracted data included but were not limited to Axis I diagnoses, treatment duration, concomitant psychotropic medications, prospectively entered Clinical Global Impression-Severity (CGI-S) and CGI-Improvement (CGI-I), weight, and ECG. Response was defined as a CGI-I of 1 (much) or 2 (very much improved) at last visit (endpoint) and no adverse events requiring discontinuation.

Results: Efficacy data were available for 36 patients (mean age 13 + 3 years, median treatment duration 17 + 13 months). Patients had the following Axis I diagnoses: bipolar disorder (68.6%); ADHD (48.6%); depressive disorder and ODD/conduct disorder (25.7% each); anxiety disorder (17.1%); Asperger's syndrome, learning disorder NOS, and Tourette's syndrome (11.4% each); schizoaffective disorder, psychotic disorder NOS, impulse control, and alcohol abuse (all <6%). Concomitant psychotropic medications included anticonvulsants, mood stabilizers, or lithium (54.3% of patients); antidepressants (54.3%); atypical antipsychotics (25.7%); stimulants or a-adrenergics (20.0%). 14.2% of patients received ziprasidone monotherapy. Overall median CGI-I was 2.5 (range 1-6), with 50% much or very much improved; 4 (11%) patients were minimally to much worse at endpoint. Responder rates were 44%, with none worsening, in antipsychotic-naïve patients (n=9); 61%, with 17% worsening, in patients switched from another atypical for weight gain (n=18); and 33%, with 11% worsening, in those switched for nonresponse (n=9). Ziprasidone was well tolerated, with CGI adverse-events scores being none to slight in 91.4% of patients. There was no significant difference between age-adjusted Z score and percentile for weight at start (Z score 1.59 + 1.09) and endpoint (1.58 + 1.05, t27 = -0.969; P=0.342), or between mean QTc at start (416 + 16.5 msec) and endpoint (414 + 15.6 msec, t14 = 0.635; P=0.537). No patient had a QTc >440 msec.

Conclusions: Ziprasidone showed efficacy and excellent tolerability in pediatric patients requiring antipsychotic therapy for a variety of psychiatric disorders, especially those with inadequate response to or weight gain with a previous atypical agent.

Source(s) of Funding: Supported by funding from Pfizer Inc.

POSTER NO. 97

OLANZAPINE VERSUS RISPERIDONE IN THE TREATMENT OF BIPOLAR I DISORDER: DETERMINANTS OF CHANGE IN SEVERITY OF BIPOLAR ILLNESS RATINGS

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Objective/Background: In a direct comparison of patients with bipolar manic or mixed episodes, olanzapine and risperidone showed similar efficacy in mania ratings (Baker, APA 2003), but olanzapine had greater efficacy on clinician global impression of severity (CGI-S). We performed a post-hoc analysis investigating possible determinants of this differential treatment effect.

Methods: This 3-week, double-blind study compared olanzapine (5-20 mg/day; N=165) to risperidone (1-6 mg/day; N=164) in manic or mixed episodes. Path analysis dissected the CGI-S treatment effect into drug effect explainable by effects on manic, depressive and extrapyramidal symptoms, measured by standard rating scales, versus other treatment effects not accounted for by rating scales. Demographic and disease characteristics were examined to determine if they were significant predictors of CGI-S improvement. Analysis of variance and regression models used change from baseline to endpoint (last observation carried forward) for all analyses.

Results: Olanzapine-treated patients achieved significantly greater improvement in CGI-S than risperidone-treated patients ($p=.014$). While changes in manic and depressive symptoms were significant predictors of the change in CGI-S (both $p<.001$), treatment effect remained statistically significant ($p=.006$) even after adjustment for change in these effects. In fact, 93% of olanzapine's superior treatment effect on CGI-S was not attributable to changes in mania, depression, or extrapyramidal symptoms. Race, gender, rapid cycling status, manic vs. mixed diagnosis, age of disease onset, and weight change were not significant determinants of CGI-S change. A significant interaction was detected between age and treatment: older olanzapine-treated patients had greater CGI improvement compared to older risperidone patients; no differences occurred between treatments for younger patients.

Conclusion: Rating scale, demographic, and illness characteristics were at most modest determinants of improvement in global illness severity. Even after adjusting for significant determinants, olanzapine-treated patients still experienced significantly greater improvement than risperidone-treated patients in global illness severity.

Source(s) of Funding: Eli Lilly and Company

POSTER NO. 98

PANDAS WITH CATATONIA: RESPONSE TO LORAZEPAM AND PLASMAPHERESIS

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Background: PANDAS (Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) is thought to result from molecular mimicry in which antibodies formed against certain serotypes of streptococcus pyogenes cross react with neuronal cells to produce inflammation in the central nervous system, particularly the basal ganglia (1, 4). Elevated antineuronal antibodies (4, 5) enlarged basal ganglia (6, 7), and response to immunomodulatory treatments (2, 7) support an autoimmune model. Catatonia is a non-specific syndrome, characterized by motoric immobility, or excessive motor activity that is apparently purposeless and not influenced by external stimuli, extreme negativism or mutism, peculiarities of voluntary movement or echolalia or echopraxia (8). Acute catatonia is known to respond to benzodiazepines(9).

Case Report: 11-year old boy without previous psychiatric history, presented with an acute need to void (leading to three hospitalizations with negative urological finding), decreased speech, periods of staring and immobilization (maintaining limb position in mid-motion), intermixed with impulsive purposeless movements, mood lability and inattention. Cognition, comprehension and receptive language were intact. Neuropsychiatric symptoms followed a fever, cough, ear infection, and sinusitis. Medical work-up was significant for elevated ASO, 282 (range 0-240 IU/mL) and DNase B antibodies1:680 (range 1:170g). MRI showed both putamina and both caudate nuclei to be significantly swollen while remainder of the brain was normal. **Treatments:** Lorazepam was started on Day 23 after onset of symptoms at 1mg. every six hours for 5 days, decreased to 0.5mg. during the next 13 days and then tapered. A total of 5 plasma exchanges were done on days 28, 31, 33, 34 and 37 after onset of symptoms. **Results:** Lorazepam Treatment: Within 24-hours after first lorazepam dose, "freezing" and "staring" episodes were eliminated, expressive language improved, and activity level decreased. Plasmapheresis treatment 1 was followed by an immediate improvement in ability to cooperate and accept redirection. Plasmapheresis treatment 2 was followed by ability to follow 3-step directions. Mood lability resolved and movements were slower and less erratic. Speech was fluent. Plasmapheresis treatments 3, 4, 5 were followed by continued decrease in overall activity level and normalization of speech and behavior.

CAUDATE AND PUTAMEN SIZE BEFORE AND AFTER PLASMAPHRESIS

	QQPre-treatment	Post-treatment	Reduction in size (%)
Rt. Caudate	9.8 cm	5.5 cm	46%
Lt. Caudate	8.4 cm	5.8 cm	31%
Rt. Putamen	13.2 cm	9.7 cm	27%
Lt. Putamen	15.6 cm	10.5 cm	33%

Within 3 weeks after last plasma exchange the youngster returned full-time to school and made honor roll four months later.

CONCLUSIONS: This is the second case report documenting basal ganglia volumetric changes that corresponded with improvement in symptoms after plasmapheresis treatment (7). Benzodiazepines were effect in treating catatonia.

POSTER NO. 99

ARE ANTIDEPRESSANTS ASSOCIATED WITH SWITCHING FROM MAJOR DEPRESSION TO MANIA IN PATIENTS WITH BIPOLAR I DISORDER?

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Objective/Background: An unresolved controversy in the treatment of bipolar depression is the extent to which antidepressant medications precipitate hypomania or mania. This concern influences the treatment of bipolar depression, causing some clinicians to advocate the minimal use of antidepressants. Some experts challenge this view, citing high rates of suicide, social and occupational dysfunction, and depressive relapse in bipolar depression. The primary objective of this study is to determine whether antidepressant medications are significantly associated with switching from major depression to mania or hypomania in subjects with bipolar I disorder.

Methods: Study subjects come from the National Institute of Mental Health Collaborative Depression Study (CDS) longitudinal observational data. They include those with Research Diagnostic Criteria bipolar I disorder or schizoaffective disorder with mainly affective mania subtype, as well as those who met criteria for non-bipolar major depressive disorder at intake but who subsequently developed an episode of mania during the 20-year follow-up. A rate of spontaneous switch from major depression to mania was estimated by identifying switches to mania, hypomania or a mixed episode during the first 8 weeks of a major depressive episode. Only subjects who received no antidepressant medication during the 8 weeks prior to the onset of the depressive episode and during the 8-week follow-up period were included in this calculation. This rate was compared to the rate of switches into mania, hypomania or a mixed episode within 8 weeks of starting a new antidepressant in subjects with bipolar I major depression, using mixed-effect logistic regression analysis. The analyses included multiple within-subject treatment intervals over the course of follow-up.

Results: The mean length of follow-up for subjects included in these analyses was 15.2 (± 4.8) years. The analyses identified 638 eligible affective episode intervals among 149 subjects who were at risk for either spontaneous and/or treatment associated affective switch. No significant difference in switch rates was observed between the 429 untreated episode intervals and the 209 antidepressant-exposed episode intervals (6.1% vs. 9.1%; odds ratio =1.81, 95% CI: 0.89-3.69; z=1.64, p=0.10).

Conclusion: To our knowledge, this the largest longitudinal observational study of antidepressant-associated affective switch in subjects with bipolar I disorder. This analysis found no significant difference in rates of switch from major depression to mania, hypomania or mixed episodes associated with the use of antidepressant medication when compared to spontaneous switches.

Source(s) of Funding: Supported in part by funding from the APIRE/Janssen Scholars in Research on Severe Mental Illness Fellowship Award

POSTER NO. 100

A COMPARISON OF DIVALPROEX, GABAPENTIN AND OXCARBAZEPINE IN AGGRESSIVE YOUTH

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Objective/Background: To compare the effectiveness of divalproex, gabapentin, and oxcarbazepine for treatment of severely aggressive youth in actual practice, where diagnosis, concomitant medications and treatment duration are complex.

Methods: 4,494 psychiatric outpatients' records were searched for patients <18 years treated with divalproex, gabapentin, or oxcarbazepine for severe aggression. Clinical Global Impressions-Improvement (CGI-I), Severity(CGI-S), and Adverse Experiences(CGI-AE) scores at 6 months and at last recorded visit were the primary outcomes. CGI data was compared using nonparametric statistics. Background variables were also considered as possible covariates in a logistic regression model. Responding was defined as a CGI-I = 2 and worsening was defined as a CGI-I = 5.

Results: 65 patients (divalproex n=29, gabapentin n=15, oxcarbazepine n=21) had baseline and treated data available. The groups did not differ with respect to sex, age, previous number and types of psychotropic trials or psychiatric diagnoses. They did not differ with respect to concomitant psychotropics at last recorded visit or at 6 months, with the exception of concomitant neuroleptic use at 6 months (divalproex 14(48.3%), gabapentin 1(6.7%), oxcarbazepine 12(57.1%); Fisher's Test, p=0.005). The divalproex group also had higher starting CGI-S scores, indicating greater starting severity (divalproex median=5(range:3-7), gabapentin 4(3-5), oxcarbazepine 4(3-6); chi square=12.0, df=2, p=0.002). Gabapentin and oxcarbazepine were associated with significantly higher rates of discontinuation due to worsening of aggression at 6 months than divalproex (divalproex 0(0.0%), gabapentin 2(13.3%), oxcarbazepine 3(14.3%); Fisher's test, p=0.02). More patients in the gabapentin group were worse overall at end of observation than in other groups (divalproex 4(13.8%), gabapentin 6(40.0%), oxcarbazepine 4(19%); Fisher's Test, p=0.046). However, the percent classified as responders at last observation did not differ significantly between groups (divalproex 16(55.2%), gabapentin 5(33.3%), oxcarbazepine 11(52.4%); Fisher's test, p=0.14). Covariates, e.g. CGI-S and concomitant neuroleptic use at 6 months, did not significantly attenuate the above results, as the odds ratios did not change appreciably when adjusted for each covariate.

Conclusion: For the treatment of aggressive youth divalproex, oxcarbazepine, and gabapentin differed most robustly in the rates of worsening aggression and discontinuation due to worsening aggression. Divalproex shows fewer discontinuations due to worsening of aggression than gabapentin and oxcarbazepine. Gabapentin is associated with greater worsening overall. These findings were not due to concomitant neuroleptic use or differences in starting CGI-S. Differences in responder rates between these agents did not reach statistical significance. Prospective controlled trials of comparative effectiveness of psychotropics for severe aggression are warranted.

Source(s) of Funding: Research grant from Abbott Laboratories

POSTER NO. 101

EXTENDED-RELEASE CARBAMAZEPINE MONOTHERAPY FOR ACUTE MANIA AND MIXED SYMPTOMS ASSOCIATED WITH BIPOLAR DISORDER

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Objective/Background: Carbamazepine (CBZ) has long been considered a standard therapy for bipolar disorder. However, until recently, CBZ had only been evaluated in small trials, which were rarely placebo-controlled, and used exclusively immediate-release preparations which need to be administered 3- or 4- times daily to avoid potentially problematic serum drug fluctuations. Extended-release formulations of carbamazepine were developed to decrease dosing frequency and to decrease plasma fluctuations associated with immediate-release formulations. A large study has been conducted to assess the acute efficacy and safety of extended-release carbamazepine capsules (ERC-CBZ; SPD417) as monotherapy in the treatment of manic and mixed bipolar disorder patients.

Methods: A 3-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study was conducted. 239 subjects (mean age 37; 30% female; 21% mixed) with a DSM-IV diagnosis of Bipolar Disorder (manic or mixed) were randomized to placebo or ERC-CBZ (initiated at 200 mg bid and increased by 200 mg/d if tolerated to a maximum daily dosage of 1600 mg). Efficacy was assessed by the YMRS, the CGI, and HDRS.

Results: One-hundred forty-four patients (60.2%) completed the study There was a statistically significant difference between the treatment groups in favor of ERC-CBZ for YMRS mean total score at endpoint ($P<0.0001$); responders (>50% reduction in YMRS, $P<0.001$); CGI severity ($P<0.001$); CGI improvement ($P<0.001$); and HDRS ($p<0.01$). The most frequently reported AEs for ERC-CBZ were dizziness, nausea, and somnolence.

Conclusion: ERC-CBZ was found to be effective for the treatment of manic and mixed symptoms in bipolar patients for up to 21 days at a titrated dose of between 200 mg and 1600 mg/d. AEs were generally mild to moderate in nature and no significant weight gain was noted.

Source(s) of Funding: Shire, Newport, KY

POSTER NO. 102

TRENDS IN ANTIPSYCHOTIC PRESCRIBING TO CHILDREN AND ADOLESCENTS: 1996 TO 2001

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Background: The purpose of this study was to examine trends in antipsychotic use in children and adolescents enrolled in three Medicaid programs (a Midwestern [MM], Southern [SM], and Western [WM] state) or a national private managed care organization (MCO); to compare prevalence rates of antipsychotic use across geographically diverse regions; and, to compare prevalence rates of antipsychotic use in public versus private payer systems.

Method: Antipsychotic prevalence was defined as the number of individuals under the age of 20 years with at least one prescription claim for an antipsychotic agent, regardless of subclass, per 1,000 enrolled children and adolescents. Total, antipsychotic subclass, age-specific, and gender-specific prevalence rates of antipsychotic use from 1996 to 2001 were estimated. Time trends of antipsychotic prevalence estimates were assessed, and logistic regression analyses were used to determine odds ratios of antipsychotic use in each system.

Results: From 1996 to 2001, the prevalence of total antipsychotic use increased in each insurance program (MM: +9.6 per 1,000, odds ratio [OR] 1.24; SM: +9.2, OR 1.19; WM: +2.4, OR 1.10; and, MCO: +2.0, OR 1.24). The prevalence of typical antipsychotic use decreased (prevalence ratios [2001:1996] 0.29 to 0.72; OR 0.78 to 0.98), while the prevalence of atypical antipsychotics dramatically increased (prevalence ratios 5.99 to 19.73; OR 1.35 to 1.56). Across all systems, the use of antipsychotics increased in children and adolescents above the age of 5 years. Male and female antipsychotic prevalence rates increased over the 6-year study period. Based upon rank order, antipsychotic usage was highest in SM, followed by MM and WM. All three Medicaid programs had higher prevalence rates of antipsychotics than the MCO.

Conclusion: In all 4 insurance programs, the prevalence of antipsychotic use in children and adolescents increased significantly from 1996 to 2001. This is primarily attributed to the increased use of atypical antipsychotics. Geographic variations in antipsychotic prescribing, as well as differences between public and private systems, existed. Given the limited efficacy and safety data with antipsychotics in children and adolescents, this raises questions about appropriate use and emphasizes the need for additional studies of atypical antipsychotics in this population.

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POSTER NO. 103

SLEEP AND MOOD IN PATIENTS TREATED FOR BIPOLAR DISORDER: A TIME SERIES APPROACH

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Objective/Background: While sleep disturbances frequently accompany mania and depression, they are also common side effects of many of the medications used to treat bipolar disorder. This study verifies the association between sleep and mood changes in medicated patients, using daily self-reported mood and sleep data from patients receiving a mean of 3.8 medications daily.

Methods: Data was received from 60 patients (41 BP I; 19 BP II) who entered a mean of 149 days into ChronoRecord software and were selected for having 2 or less sequential days of missing data. For each patient, mood and sleep data was pre-whitened using an ARIMA (0,1,1) model to remove trends and establish stationarity. The relationship between mood and sleep over time was determined using cross-correlation analysis. By diagnosis, patients with and without significant cross-correlations were compared using a univariate linear mixed model.

Results: 23 patients (16 BP I, 7 BP II) showed significant inverse cross-correlations between mood and sleep at a lag of 0. 37 patients (25 BP I, 12 BP II) did not show any significant cross-correlations. Those showing significance were manic/hypomanic (p=.011) more frequently, reported more severe symptoms of mania (p=.041), reported more switches in mood from normal to mania/hypomania (p=.029), mania/hypomania to depression (p=.006), depression to mania/hypomania (p=.015), took more medications (p=.002) and were more likely to receive a government disability (p=.037).

Conclusion: Despite receiving multiple medications, patients who are symptomatic for bipolar disorder still have sleep disturbances when manic or depressed.

Source(s) of Funding: UCLA Department of Psychiatry

POSTER NO. 104

ACUTE WEIGHT GAIN WITH COMBINATION DIVALPROEX SODIUM AND OLANZAPINE IN CHILDREN AND ADOLESCENT INPATIENTS AT A UNIVERSITY HOSPITAL

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Objective/Background: Weight gain associated with antipsychotics and mood stabilizers is a common problem associated with their use in psychiatric patients. There is some evidence that this effect may be more robust in children and adolescents. Reasons for this effect are not yet clear nor or a definitive mechanism for the effect established. It is common to use combination therapy in the acute and maintenance phase of many psychiatric disorders in children. Although the benefits of combination therapy have been established, the side effect burden has not been adequately studied. Divalproex sodium and olanzapine are often used together, primarily in mood disorders. Although numerous studies have evaluated the weight gain with each of these agents separately in adults, this analysis evaluated the acute weight changes of this combination in a younger patient population.

Methods: A retrospective chart review was conducted on 148 children and adolescent inpatients that received olanzapine therapy during their hospitalization with 112 of these patients initiated with olanzapine. Olanzapine , olanzapine and divalproex sodium, and divalproex sodium alone were examined for acute weight changes during the hospitalization. A control group of ziprasidone patients, alone and in combination with divalproex sodium, were compared. Age, gender, diagnosis, and concomitant medications were also evaluated.

Results: Patients ranged in age from 6-18 years with a mean age of 13.1 years. Sixty-eight percent were male with the most common diagnosis Bipolar Disorder NOS. The combination of olanzapine and divalproex sodium produced significant weight gain within the first week of therapy. This weight gain was present early in the majority of patients receiving this combination. It appeared even in the presence of weight lowering agents and led to discontinuation in a percentage of the patients. In contrast, our control groups of ziprasidone and ziprasidone plus divalproex sodium produced minimal acute weight gain.

Conclusion: Significant weight gain was observed early when combination therapy of olanzapine and divalproex sodium was used in hospitalized children and adolescents. Weight gain in this at risk patient population was rapid and robust. This may be related to the additive effects of acute insulinemia and possibly an increase in ratio of olanzapine to desmethylolanzapine. The exact mechanism and how this translates into longer-term therapy needs to be further established.

Source(s) of Funding: The Ohio State University Residency Program.

POSTER NO. 105

RISK OF MOVEMENT DISORDERS IS LOW IN PEDIATRIC PATIENTS TREATED WITH RISPERIDONE

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Background: Antipsychotic agents have a definite role in the treatment of children and adolescents with psychiatric disorders. The use of these agents is limited, however, by their association with acute and tardive movement disorders, although emerging data suggest that atypical antipsychotics have a reduced potential for inducing extrapyramidal symptoms in comparison with conventional agents. Several recent, well-controlled studies have demonstrated that the atypical antipsychotic risperidone is safe and efficacious in pediatric patients with disruptive behavior disorders (DBDs). The objective of this analysis was to assess the risk of acute and tardive movement disorders in a large dataset of pediatric patients with DBDs receiving risperidone treatment.

Methods: Data were from 2 1-year, open-label extensions of short-term, placebo-controlled trials, and a third 1-year open-label study. Dyskinesia was defined as 2 or more scores of 2 or 3, or 1 score of =4, on the Extrapyramidal Symptom Rating Scale (ESRS) dyskinesia subscale (E51-E57). Tardive dyskinesia (TD) was defined as dyskinesia at 2 or more consecutive visits in patients without dyskinetic symptoms at baseline (all 7 ESRS dyskinesia items equal 0 or 1). Symptoms were evaluated at baseline, Weeks 1-4, 8, 12, 16, 20, 24, 36, 48, and at endpoint.

Results: Data were available for 663 patients (mean age, 9.44 years; 81.7% male; mean IQ, 64.8). ESRS scores generally were low throughout the study. Among the 651 patients without dyskinetic symptoms at baseline, 2 (0.3%) patients met the predefined TD criteria during the study. Both cases resolved with continued treatment, demonstrating that these were reversible dyskinesia cases. Twelve patients had dyskinesia at baseline. At endpoint, the mean severity of symptoms in these 12 patients had decreased.

Conclusions: The risk of movement disorders is an important consideration in choosing among antipsychotic drugs. Treatment with the atypical antipsychotic risperidone was found to be associated with a low risk of acute and tardive movement disorders in pediatric patients with DBDs in 3 large 1-year studies.

Disclosure: Supported by Janssen Pharmaceutica Products, L.P.

POSTER NO. 106

EFFICACY OF INDIPLON-MR IN INDUCING AND MAINTAINING SLEEP IN PATIENTS WITH CHRONIC SLEEP MAINTENANCE INSOMNIA

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Background: Indiplon is a GABA potentiator with selectivity for receptors with the alpha-1 sub-unit. The modified release (MR) formulation, indiplon-MR, has been developed to provide rapid absorption and onset of activity, maintenance of therapeutic blood levels throughout the night, and clearance from plasma to avoid next day residual effects. The current study was designed to evaluate the efficacy and safety of indiplon-MR for the treatment of sleep maintenance insomnia.

Methods: Adult outpatients who met DSM-IV criteria for primary insomnia for >3 months, with usual total sleep time <6.5 hours and wakefulness after initial sleep onset >0.75 hours, completed a 2-week placebo lead-in, and then were randomized to 2 weeks of double-blind indiplon-MR 30mg or placebo (68% female; mean age, 48 years). The primary endpoint was subjectively rated total sleep time (sTST); additional endpoints included latency to sleep onset (LSO), subjective wake time and number of awakenings after sleep onset (sWASO; sNAASO), sleep quality, patient global impression (PGI), and investigator global ratings of severity and change (IGR-S; IGR-C).

Results: As summarized in the Table, indiplon-MR resulted in significant improvement compared to placebo in both the primary endpoint (sTST) and in secondary endpoints.

	Placebo (N=104)	Indiplon-30mg (N=102)
Total sleep time (sTST)		
Week 1	**327.6 min**	**375.0 min*** **
Week 2	**336.3 min**	**366.9 min** **
Awake after sleep onset (sWASO)		
Week 1	**79.1 min**	**52.3 min*** **
Week 2	**73.4 min**	**52.1 min**
Latency to sleep onset (LSO)		
Week 1	**37.4 min**	**29.4 min** **
Week 2	**35.3 min**	**27.9 min* **
# of awakenings after sleep onset (sNAASO)		
Week 1	**1.93**	**1.24*** **
Week 2	**1.83**	**1.24*** **
Sleep quality 1		
Week 1	**4.2**	**3.6*** **
Week 2	**4.1**	**3.5*** **

[1]Patient-rated scale of 1 (extremely good) to 7 (extremely poor); *p<0.05;**p<0.01;***p<0.0001

Indiplon-MR was found to be to be significantly superior to placebo (p<0.0001) on the PGI, as well as on the IGR-S and IGR-C (p<0.0001). There were no differences between indiplon-MR vs. placebo in next day drowsiness or daytime functioning.

Conclusions: In this study of patients with chronic sleep maintenance insomnia, indiplon-MR demonstrated significant efficacy in inducing and maintaining sleep, with significant improvements in sleep quality. Improvements in sleep parameters were accompanied by significant changes in patient and investigator global ratings of efficacy. Indiplon-MR 30mg was well-tolerated with no evidence of drowsiness or impaired ability to function the next day, relative to placebo.

Source of funding: Neurocrine Biosciences, Inc.

POSTER NO. 107

RECRUITMENT OUTCOMES IN CHILD AND ADOLESCENT DEPRESSION TRIALS

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Background: Since the inclusion of the Pediatric Rule into the Code of Federal Regulations (CFR), sponsors must include pediatric assessments in the submission of a New Drug Application (NDA). Successful completion of this task can yield a 6-month patent life extension for a FDA approved medication resulting in millions of dollars in increased revenue. It also can provide valuable prescribing information for clinicians who must otherwise attempt to extrapolate data from adult trials. However, because of the pharmacodynamic and pharmacokinetic differences between children and adults, extrapolation is often very difficult. Recent warnings from the FDA about the incidence of suicidal behavior in pediatric depression underscores the importance of conducting more studies in this population in particular. Subsequently, we analyzed recruitment methods for pediatric depression trials in an effort to provide further insight into more effective ways to enroll children and adolescents in these critical trials.

Methods: Data from our three most recent pediatric depression trials were assessed for recruitment methods and outcomes. Pre-screening visits from 101 children and adolescents with depression were analyzed to determine the referral source of the potential subject and their respective screening, randomization, and completion status. The referral sources were divided into five categories: television commercial, radio commercial, print advertisement, direct referral, and national campaigns. For each category, the number of prescreens, screening visits, randomizations, completed patients was stratified.

Results: The 101 prescreen visits resulted in 51 screening visits, 30 randomizations, and 20 completed subjects. Collectively across all five recruitment methods, 50% of prescreens were screened, 59% of screens were randomized, and 63% of the randomizations completed the trial. Radio, print, and direct referral sources each contributed approximately 30% of the subjects who were screened, with television and national campaigns contributing the remainder. Of subjects who completed the trial, 42% were from print, 26% from direct referrals and radio, and 6% from national campaigns.

Conclusion: In three consecutive pediatric depression trials, site-managed print and radio advertisements proved to be at least as effective as direct referral sources in producing completed subjects. Surprisingly, television advertisements were not an effective means of subject recruitment. National advertising campaigns, which can be very effective for a number of other indications, were not effective in this population. A more in depth look at the integration of site recruitment practices with national campaign methods may provide useful strategies to increase enrollment with these large scale campaigns in pediatric depression. Further analysis of other variables such as frequency of advertising, timing of these events, and cost may yield further information to help expedite the recruitment process of these vitally important trials.

POSTER NO. 108

THE SAFETY AND EFFECTIVENESS OF SERTRALINE FOR THE TREATMENT OF NEURASTHENIA

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Objective/Background: Objectives 1. Understand the diagnostic importance of Neurasthenia among Asian Americans 2. Assess the utility of using a selective serotonin reuptake inhibitor (SSRI) for the treatment of neurasthenia. Neurasthenia is a cultural syndrome that is diagnosed commonly in East Asian countries, and has been seen as a cultural variant of depression. However, the syndrome is distinct in that it is not necessary to have mood symptoms, and instead has fatigue as its core symptom. There are no published studies that have assessed the safety and effectiveness of using an SSRI for its treatment.

Methods: Subjects (18-65 yrs of age) who met diagnostic criteria for neurasthenia with or without depression and/or dysthymia were enrolled in a 13 week open label study with flexible dosing of sertraline 50 -200 mg. The primary efficacy measures were the CGI-I, and the Multidimensional Assessment of Fatigue Questionnaire (MAFQ). Secondary measures included the Patient Health Questionnaire, Somatic Symptoms Inventory, Hamilton Anxiety Scale, and the Quality of Life, Enjoyment, and Satisfaction Questionnaire.

Results: 19 subjects were available for baseline to endpoint intent-to-treat analysis. The mean CGI-I mean change score was -1.9 SD 1.2, ($p < 0.0002$), 47% of subjects were CGI-I responders (CGI-I less than or equal to 2). The mean MAFQ change score was -20.2 SD 18.1 ($p < 0.0001$). In the completer subgroup (n=10), the mean change in CGI-I was -1.9 SD 1.2, ($p < 0.0007$) and 80% were CGI-responders. The mean MAFQ change score was -29.4 SD 18.1, ($p < 0.0006$). 2 subjects discontinued the study due to adverse events and no serious adverse events occurred.

Conclusion: Sertraline was generally well tolerated and effective for the treatment of neurasthenia in this pilot study. A larger, controlled study should be performed to confirm these findings.

Source(s) of Funding: Investigator initiated research grant from Pfizer, Inc.

POSTER NO. 109

SAFETY AND EFFICACY OF METHYLPHENIDATE FOR PERVASIVE DEVELOPMENTAL DISORDERS: AN OPEN LABEL STUDY

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Objective/Background: There is a substantial rate of prescribing of methylphenidate (MPH) for children and adolescents with Pervasive Developmental Disorders (PDD) combined with hyperactivity, inattention and impulsivity. However, the use of MPH for PDD subjects is mainly based on anecdotal data, as research in this area has been limited and results have been conflicting. In particular the clinical literature suggests that a sizable proportion of children with PDD may be susceptible to adverse responses to these medicines. This study investigates the effects of chronic MPH on ADHD-related and autistic symptoms in PDD, after an acute test dose administered in the clinic.

Methods: Participants were 13 subjects (12 males, mean age 7.9 years) with DSM-IV PDD and moderate to severe hyperactivity/impulsivity. After parental informed consent, all subjects received a single MPH dose (0.4 mg/kg). Between one and two hours after drug administration subjects were rated. Those who were rated "worse," including "minimally worse," on the Clinical Global Impression (CGI)-global improvement scale received no further treatment. Those rated as unchanged up to very much improved proceeded to a 12-week open trial of MPH. Severity of symptoms assessment was based on CGI, Childhood Autism, Child Psychiatric and Conners parent and teacher rating scales. Tolerability was measured with the Abnormal Involuntary Movement Scale, and a side effect checklist monitoring most frequent MPH side effects. Scores at baseline and after 1 and 3 months of treatment were compared with intent to treat analysis by using the last observation carried forward model.

Results: One hour after a single MPH dose, five subjects exhibited increased hyperactivity, stereotypies, dysphoria, or motor tics and were rated as minimally or much worse on the CGI Global Improvement Scale. They received no further treatment with MPH. Four of the remaining subjects were rated as improved, and four as unchanged; they proceeded to a 12-week open trial of MPH. In group analyses, behavioral measures of hyperactivity and impulsivity improved significantly, while autism core symptom measures were unaffected. However, two children remained unchanged and discontinued treatment after 1 week on maximally tolerated doses. No significant adverse effects were observed in any of the eight subjects.

Conclusion: A subgroup of subjects with Pervasive Developmental Disorders can benefit from chronic treatment with MPH. Administering a single MPH test dose in the clinic may be useful in identifying children with PDD who may benefit from chronic methylphenidate treatment.

Source(s) of Funding: No external funding

POSTER NO. 110

AN OPEN-LABEL TRIAL OF ESCITALOPRAM FOR MAJOR DEPRESSION IN HEPATITIS C

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Objective/Background: Hepatitis C affects nearly 4 million Americans. Depression is a common comorbid condition among this population and may be induced by interferon alpha, an approved treatment for hepatitis C. Development of depression during treatment is a major cause of discontinuation of interferon therapy. This research-in-progress aims to examine the effect of escitalopram on measures of depression, quality of life and tests of liver function in subjects with hepatitis C and major depression.

Methods: Hamilton Depression Rating Scale (HAM-D) scores, Clinical Global Impression (CGI) scores, Medical Outcomes Study Short Form Health Survey (SF-36) ratings, Symptom Checklist- 90 (SCL-90) scores and liver function tests were obtained at baseline, 2 weeks, 4 weeks and 8 weeks.

Results: To date, 18 subjects (12 female, 6 male) have participated in this study. The mean daily dose of escitalopram at endpoint was 12.78 milligrams. Mean HAM-D (17-item) scores have decreased significantly with treatment ($t=8.928$, $DF=17$, $p < 0.0001$). Statistically significant improvement has also been demonstrated on several subscales of the SF-36 (emotional well-being ($t=-4.922$, $DF=13$, $p=0.0003$), pain ($t=-3.148$, $DF=13$, $p=0.0077$), emotional functioning ($t=-2.870$, $DF=13$, $p=0.0131$)) and SCL-90 (interpersonal sensitivity ($t=4.567$, $DF=13$, $p=0.0005$), depression ($t=4.355$, $DF=13$, $p=0.0008$) anxiety ($t=4.085$, $DF=13$, $p=0.0013$), anger and hostility ($t=3.821$ $DF=13$ $p=0.0021$), somatization ($t=3.78.2$, $DF=13$, $p=0.0023$). Liver function tests have shown no statistically significant change from baseline to visit week 8.

Conclusion: These results suggest that depression in patients with Hepatitis C may be effectively and safely treated with escitalopram.

Source(s) of Funding: Forest Pharmaceuticals

POSTER NO. 111

POLYPHARMACY AMONG CHILDREN AND ADOLESCENTS TREATED IN ROUTINE PSYCHIATRIC PRACTICE

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Objectives: To assess rates and correlates of concomitant pharmacotherapy in children and adolescents treated by psychiatrists in the full range of public and private treatment settings.

Methods: This study examines psychiatrist-reported cross-sectional clinical data for a national sample of 392 psychiatric patients under 18 years of age from the 1997 and 1999 APIRE Practice Research Network (PRN) Study of Psychiatric Patients and Treatments. Patients were systematically selected by psychiatrists participating in the APIRE PRN. Data were weighted to provide nationally representative estimates. In this study concomitant pharmacotherapy is defined as the concurrent use of two or more psychotropic medications for the treatment of emotional or behavioral problems in children and adolescents (Safer, Zito, dos Reis 2003).

Results: Findings indicate that 84.5% of child and adolescent patients treated by psychiatrists received one or more psychotropic medications for the treatment of emotional or behavioral problems; 41.6% of these 392 patients received concomitant pharmacotherapy. Patients on psychopharmacologic treatments received an average of 1.8 medications (range=1 to 6). Significantly higher rates of concomitant pharmacotherapy were observed among patients with bipolar disorder than those without (86% vs. 47%; $p<0.001$), patients with CGAS score of 50 or less than those with CGAS greater than 50 (65% vs. 47%; $p<0.01$), patients with a history of hospitalization than those never hospitalized (69% vs. 46%; $p<0.01$), patients with one or more Axis I (59% vs. 42%; $p<0.05$), Axis II (73% vs. 50%; $p<0.05$), or Axis III comorbidities (68% vs. 48%; $p<0.05$), or two or more Axis IV psychosocial problems (57% vs. 34%, $p<0.05$), and among patients with public insurance in contrast to those with private, selfpay, or other insurance (65%, 50%, 42%, 28% respectively; $p<0.05$).

Conclusion: The majority of child and adolescent patients of psychiatrists were treated with psychotropic medications, and four out of every ten patients received two or more psychotropic medications. Given that the available evidence base for pharmacological treatment of most psychiatric disorders in children and adolescents lags behind that for adults, attention needs to be directed toward treatment strategies that are lacking in evidentiary support in this patient population. With high rates of concomitant pharmacotherapy among children and adolescents in psychiatric care, research on efficacy and safety for this treatment strategy is of utmost importance. Findings of this study will inform longitudinal practice-based clinical effectiveness studies with larger sample sizes to examine patterns, quality and outcomes of psychopharmacologic and concomitant pharmacotherapy in children and adolescents.

Sources of Funding: The American Psychiatric Foundation; the Center for Mental Health Services; the Center for Substance Abuse Treatment, and the John D. and Catherine T. MacArthur Foundation.

POSTER NO. 112

DEXTOFISOPAM: A NOVEL HOMOPHTHALAZINE WITH POTENTIAL FOR TREATMENT OF STRESS-RELATED DISORDERS

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Vela Pharmaceuticals Inc.

Objective: To characterize dextofisopam, the R-isomer of racemic tofisopam, we conducted a series of nonclinical studies as well as trials in healthy volunteers.

Methods: Dextofisopam was tested in animal models of stress-related autonomic dysfunction, including functional gastrointestinal disorders (primarily IBS). Two randomized, double-blind, placebo-controlled, Phase 1 clinical trials were also completed. In the first study, 42 subjects received single doses of dextofisopam (50 mg, 100 mg, 200 mg, 300 mg, or 400 mg) or placebo. In the second study, 45 subjects received dextofisopam (100 mg TID, 150 mg TID, 200 mg TID, 400 mg BID, or 600 mg BID) or placebo for 7 days.

Results: In nonclinical studies, dextofisopam reduced stress-induced ulcer formation, normalized stretch-induced colonic contraction, and reduced visceral hypersensitivity, with little effect on basal colonic motility. Dextofisopam was also active in models of inflammation, including the dextran sulfate sodium treated rodent, LTB4-induced skin inflammation, arachidonic acid-induced skin inflammation, and adjuvant-induced arthritis.

Dextofisopam was generally well tolerated up to the highest dose level in both clinical studies, with no serious or severe AEs and minimal impact on cognitive or motor function. AEs were similar with dextofisopam or placebo.

With single or multiple doses of dextofisopam, Cmax was reached approximately 1 hour after administration regardless of dose. With single doses, Cmax and AUC increased with dose in a roughly linear manner, although the Cmax values were somewhat less than expected for the 50 and 300 mg doses. Mean t½ appeared to lengthen with increasing dose, from 1.6 hours at 50 mg to 10.2 hours at 400 mg. With multiple doses, mean t½ ranged from 4.8 to 10.1 hours, appearing to be relatively independent of dosage through 400 mg BID, but increasing with the 600 mg BID dosage. These preliminary data supported greater potential for accumulation with TID than with BID dosing.

Conclusions: Dextofisopam demonstrated significant activity in animal models of stress, functional gastrointestinal disorders, and inflammation. These data, combined with the benign safety profile of dextofisopam in healthy human volunteers, support the potential of dextofisopam for the treatment of stress-related disorders, including IBS and IBD. A placebo-controlled Phase II study in patients with IBS is currently ongoing.

Source of Funding: Research supported by Vela Pharmaceuticals Inc.

POSTER NO. 113

TREATMENT-REFRACTORY CHILDHOOD SCHIZOPHRENIA: CHANGES IN GLUCOSE AND LIPID LEVELS ASSOCIATED WITH ATYPICAL ANTIPSYCHOTICS

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Objective/Background: In younger adult patients with schizophrenia, clozapine administration has been associated with a significantly increased relative risk of diabetes and hyperlipidemia (Lund et al., 2001). Prospective randomized trials in adult patients with schizophrenia or schizoaffective disorder treated with olanzapine and clozapine have documented increases in serum cholesterol and plasma glucose levels after 14 weeks of treatment (Lindenmayer et al., 2003). In this study, the authors' goal was to assess whether we would observe increases in glucose and cholesterol levels after 12 weeks of treatment in treatment-refractory adolescent patients with schizophrenia or schizoaffective disorder treated with clozapine or "high-dose" olanzapine (up to 30 mg/d).

Methods: As of January 2004, 30 children (ages 12 to 17) were enrolled in this ongoing, 12-week, multi-site, random assignment, double-blind trial. All of the children had considerable antipsychotic medication exposure prior to randomization into the study. To date, 19 children have completed 12 weeks of treatment. Planned assessments included body mass index, fasting glucose, cholesterol and triglycerides that were collected at baseline and weekly thereafter during the 12-week study period.

Results: At baseline, 8/17 (47%) patients had a BMI > 28; 4/18 (22%) had an elevated fasting plasma glucose value; 3/18 (17%) had an elevated cholesterol level; and 4/18 (22%) had an elevated triglyceride level. However, by week 12, 9/17 (53%) of patients had a BMI > 28; 0/18 (0%) had an elevated fasting plasma glucose value; 7/18 (39%) had an elevated cholesterol level; and 6/18 (33%) had an elevated triglyceride level. During the 12-week trial, no significant increases in mean BMI ($p = 0.504$), mean plasma glucose levels ($p = 0.542$), mean serum cholesterol levels ($p = 0.145$), and mean triglyceride levels ($p = 0.931$) were observed.

Conclusion: These preliminary data suggest that a significant proportion of treatment-refractory adolescents with schizophrenia referred to this study were clinically obese and already starting to show early signs of abnormalities in glucose and lipid values. In this study cohort, clozapine and "high-dose" olanzapine treatment were not associated with additional increases in plasma glucose or cholesterol levels. Early and more aggressive strategies are needed to limit these adverse events in this group of adolescents who are likely to require long-term antipsychotic treatment.

Source(s) of Funding: National Institute of Mental Health, RO1-MH60004-01; Treating Refractory Childhood Schizophrenia, John Kane, M.D., PI

POSTER NO. 114

GROUP EDUCATION IN VETERANS WITH HEPATITIS C

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Objectives: The Hepatitis C virus (HCV) infects over 4 million people in the US. Studies have found significant gaps in HCV patients' knowledge of their disease (Stein, 2001). This study assesses short- and long-term knowledge retention from a group education class for veterans with HCV.

Methods: The 1.5-hour HCV class featured a narrated slide show. Of 133 attendees, 111 consented to study participation. Identical pre-class, post-class, and long-term follow-up HCV knowledge tests contained 50 multiple-choice questions in three sub-categories: symptoms, transmission, and treatment. A self-report Patient Screening Questionnaire (PSQ) and the Beck Depression Inventory 2nd edition (BDI-II) assessed psychiatric and substance use (SU) co-morbidity.

Results: One hundred five veterans completed both pre- and post-test at the class, and to date, 29 completed a follow-up test. The sample was 93% male and 78% Caucasian, with a mean age of 52. Eighty-nine percent reported a history of psychiatric disorder, 70% two or more. Twenty-eight percent reported current hazardous alcohol use, 49% a history of drug abuse.

From pre- to post-test, total score improved significantly (51% vs. 82%; $p < .001$), as did all sub-categories: symptoms (51% vs. 79%; $p < .001$), transmission (67% vs. 88%; $p < .001$), and treatment (29% vs. 75%; $p < .001$). Demographic variables, history of psychiatric or SU disorders, and current BDI-II score were not significantly related to pre- or post-test scores, or improvement in scores.

Follow-up tests occurred an average of 76 days after the class. Mean total score and all sub-category scores improved significantly from pre-test to follow-up test ($p < .0001$). Although scores significantly declined from post-test to follow-up test in total score and in HCV symptoms and HCV treatment, they did not decrease significantly in HCV transmission, and all areas remained significantly improved from pre-test. Veterans reporting a history of psychiatric or substance related disorders did not differ significantly in knowledge retention at follow-up than did other patients.

Conclusions: A 1.5-hour group education class significantly improves patient HCV knowledge. Information on HCV transmission may be better retained than other areas, possibly preventing new infections. Knowledge improvement and long-term retention do not vary by demographic variables or history of psychiatric and substance related disorders. This suggests that a single class adequately serves most populations as a simple and cost-effective way to educate newly diagnosed HCV patients.

POSTER NO. 115

A STUDY OF OXCARBAZEPINE IN THE TREATMENT OF DISRUPTIVE BEHAVIORS OF CHILDREN AND ADOLESCENTS.

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Background: There is evidence in clinical practice that anticonvulsants are helpful for disruptive behavior disorders (DBD) of children, adolescents and geriatrics. There are no studies using the new generation anticonvulsants in children and adolescents. Oxcarbazepine is a new generation anticonvulsant, which has been shown to have positive effects on mood. It is also cleared renally and requires no blood levels.

The primary objective of this study was to measure the effect of oxcarbazepine in improvement in symptoms (i.e. aggression, agitation, explosive outbursts) at six weeks following the initiation of treatment with oxcarbazepine, as measured by the Modified Overt Aggression Scale (MOAS).

Methods: This was an open-label, outpatient, six-week treatment study. Oxcarbazepine was given to all qualifying subjects at the baseline visit with a starting dose of 150mg b.i.d. for three days, and increased by 150mg b.i.d. every four days to a daily maximum of 1200mg b.i.d., if tolerated by the subject, and at Investigator's judgment.

Criteria for inclusion included children aged 7 - 17, inclusive, with a history of Disruptive Behavior Disorders fulfilling DSM-IV-TR diagnostic classification for Conduct Disorder, Oppositional Defiant Disorder or Disruptive Behavior Disorder, NOS.

Results: Seventeen patients were screened, 14 were enrolled and received oxcarbazepine, and 10 patients completed the study. Two patients were discontinued due to adverse events (dizziness and weight gain), and 2 due to lack of efficacy. Most patients were male (71%) and Caucasian (79%), with a mean age of approx. 12 years.

At week three of treatment, 86% of patients demonstrated =50% improvement on the MOAS. At week six 71% of patients demonstrated a =50% improvement on the MOAS, a 15% decline from week three. Two of the patients who demonstrated =50% reduction by week three subsequently relapsed by week six.

Conclusions: The overall side effect profile of oxcarbazepine was fairly benign. The most frequently reported side effects were drowsiness, dizziness, insomnia, and difficulty awakening in the morning.

In summary, oxcarbazepine was well tolerated. Though the study was not placebo-controlled, nor powered for clinical significance, efficacy was observed by week three with some decline by week six. Further double- blind, placebo-controlled trials in this area will be needed to establish the efficacy of oxcarbazepine in this complicated population.

Source of Funding: Funding for this Investigator-initiated study was provided by Novartis Pharmaceuticals.

POSTER NO. 116

EXPLORATION OF THE EFFECT OF SMOKING CESSATION/REDUCTION ON THE POSITIVE, NEGATIVE AND GENERAL PSYCHIATRIC SYMPTOMS OF PATIENTS ON ANTIPSYCHOTIC MEDICATIONS

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Objective/Background: Nicotine increases dopamine (DA) levels in the brain, particularly the pre-frontal cortex. This region is generally believed to be involved in attention, concentration and executive functioning regulation and is generally an area of dysfunction in persons with schizophrenia. Previous research has suggested that persons with schizophrenia may utilize nicotine intake as a form of self-medication in an attempt to increase DA activity and improve cognitive functioning. While increasing DA in the pre-frontal cortex, smoking may also have a negative effect on the efficacy of neuroleptic medications, whereby exacerbating symptoms of the disorder. The potential for exacerbating symptoms has contributed to reservations in implementing smoking bans in some inpatient facilities. The current study examines the relationship between smoking cessation/reduction on the symptom presentation in patients on antipsychotic medications.

Methods: The current study is a 15 patient subset of a larger study focused on examining the effectiveness of transdermal nicotine treatment. Eighteen- to sixty-year-old male/female smokers (20--50 cigarettes per day) receiving antipsychotic therapy were recruited. Treatments were divided into 4 steps, with Step 1 lasting six weeks, and steps 2-4 lasting two weeks each. Active nicotine patch treatment was tapered at each new step with total cessation by week 12. Subjects were seen weekly for the first 12 weeks, with additional follow-up at week 14 and week 24. Patient self report of cigarette consumption was obtained weekly and their clinical presentation was rated at weeks 0, 2, 4, 6, 8, 12, 14, and 24.

Results: Differences between baseline and subsequent week's PANSS scores (Positive, Negative, General Psychiatric and Total Scores) were examined using paired sample t-tests. No significant differences were observed between Positive or Negative PANSS scores at baseline and subsequent weeks, except on positive symptoms at Wk 8 (positive $t=2.803$, $p<.02$). Differences between baseline and subsequent ratings of General Psychiatric Symptoms were significant at weeks 2, 4, 8 and 24. Differences between baseline and a reduction in PANSS Total scores were significant at weeks 2, 4, 6, 8 and 24

Conclusion: A decrease in nicotine consumption was not found to be strongly associated with a change in positive or negative symptom presentation, but was related to a significant decrease in general psychiatric symptoms. These findings suggest that nicotine's effect on pre-frontal DA levels is negligible in affecting changes in positive or negative symptom presentation. Furthermore, concerns about smoking bans were not supported and may actually improve overall symptom presentation.

Source(s) of Funding: UC TRDRP Grant. 10RT-0021, Steven De Luna was supported by R25 GM62252 (MBRS RISE) to Laura Robles, Ph.D. at California State University Dominguez Hills

POSTER NO. 117

EFFICACY OF SERTRALINE IN AN ANXIOUS SUBGROUP OF YOUTHS WITH MAJOR DEPRESSION

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Objective/Background: In childhood depression, little is known about treatment response in various clinically meaningful subgroups. The goal of this analysis was to evaluate the efficacy of sertraline in depressed youths with above average anxiety.

Methods: This is a secondary analysis of combined data from 2 previously reported 8 week, double-blind studies of sertraline (N=189; 43% male; 46% ages 6-11; mean baseline Children's Depression Rating Scale-revised [CDRS-R], 64.3) vs. placebo (N=187; 55% male; 49% ages 6-11; mean baseline CDRS-R, 64.6) in MDD. The anxious-depression subtype, based on normative data, by a baseline MASC total score > 51 (males) and > 58 (females). Primary assessment of efficacy consisted of LOCF-endpoint change in the CDRS-R scale and CGI-I responder status (CGI-I score < 2).

Results: For depressed patients meeting MASC criteria for above average anxiety symptoms (N=161; 43% of the total sample), treatment with sertraline resulted in significantly greater efficacy than placebo on the CDRS-R (-30.0 + 1.6 vs. -25.2 + 1.6; $p<0.05$). The antidepressant effect size for patients with above average anxiety was somewhat larger than the effect size for the total sample.

Conclusion: Sertraline demonstrates efficacy in depressed youths with above average symptoms of anxiety. In order to optimize treatment response in childhood depression, more research is needed that evaluates the benefits of antidepressants on clinically meaningful subgroups.

Source(s) of Funding: Pfizer Inc.

POSTER NO. 118

SUBJECTIVE VERSUS OBJECTIVE MEASURES OF COMPLIANCE TO A TRANSDERMAL SMOKING CESSATION PROGRAM AMONG PATIENTS ON ANTIPSYCHOTIC MEDICATIONS

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Objective/Background: Smoking is the leading cause of preventable deaths in the United States and is linked to a number of diseases, including coronary heart disease. Seventy-five percent of adults with schizophrenia are smokers compared to only twenty-five percent of adults generally. Self-reported cigarette consumption is a commonly used clinically as a measure of smoking status and need for intervention. However, utilization of self-report as a measure of treatment compliance has its inherent limitations, such as patient approval seeking, inaccuracy in recording/reporting of consumption and the denial of negative behaviors. These issues are further complicated in the schizophrenic population due to the cognitive deficits of the disorder. In order to evaluate the accuracy and utility of self-report, patient reported cigarette consumption was compared to their carbon monoxide (CO) levels and CYP1A2 molar ratio (MR).

Methods: The current study is a 15 patient subset of a larger study focused on examining the effectiveness of transdermal nicotine treatment. Eighteen- to sixty-year-old male/female smokers (20--50 cigarettes per day) receiving antipsychotic therapy were recruited. Treatments were divided into 4 steps, with Step 1 lasting six weeks, and steps 2-4 lasting two weeks each. Active nicotine patch treatment was tapered at each new step with total cessation by week 12. Subjects were seen weekly for the first 12 weeks, with additional follow-up at week 14 and week 24. At each visit carbon monoxide levels and patients self report of cigarette consumption was obtained. CYP1A2 MR was obtained weeks 0, 2, 6, 12, 24.

Results: The relationship between self-report and CO levels were compared using correlation coefficients for each follow-up visit. These measures were significantly correlated for weeks 1-6 and 8-24. These correlations ranged from .562 ($p<.05$) to .851 ($p<.01$), with most between .64 and .78. Self-report was significantly correlated with MR at week 12 ($r=.651$, $p<.02$) and week 24 ($r=.551$, $p< .03$).

Conclusion: Self-report and CO measures of compliance among patients on antipsychotic medications were found to be moderately to highly correlated. However, these measures were not significantly correlated at baseline when participants' cigarette consumption was highest. This result likely reflects the sensitivity of CO measures to recent cigarette consumption. Although CYP1A2 MR was shown to be correlated with smoking status, this significance was not observed until weeks 12 and 24, possibly due to time lag in the reversal of the inductive effects of this enzyme.

Source(s) of Funding: UC TRDRP Grant. 10RT-0021, Steven De Luna was supported by R25 GM62252 (MBRS RISE) to Laura Robles, Ph.D. at California State University Dominguez Hills

POSTER NO. 119

A COMPARISON OF RISPERIDONE-INDUCED WEIGHT GAIN ACROSS THE AGE SPAN

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Objective: To determine the extent of weight gain induced by risperidone (RIS) across the entire age span, a systematic and comprehensive literature search was performed.

Methods: The review included weight related data from all published studies of RIS treatment in youths (n=36) and geriatric subjects (n=9), and similar data from large studies (n=15) of middle-aged adults. Studies included double-blind trials, open trials and case series findings that contained data on drug dose, mean or median age of subjects, weight gain, duration of RIS treatment, and if available, baseline body weight (BBW), body mass index (BMI), and the percent of subjects with a prominent RIS-induced weight gain. Drug-induced weight gain per month for youths was defined as the recorded weight gain minus the age-expected weight gain.

Results: The major findings from the pooled data analyses were: 1) preadolescent youths received a smaller average daily dose and lower mg/kg/day dose of RIS than adolescents, and adolescents in turn had lower mg/kg/day doses than middle-aged adults 2) RIS-induced weight gain as a percentage of baseline body weight was most pronounced in the preadolescent years and decreased with advancing age 3) adults over age 65 experienced little to no RIS-induced weight gain 4) RIS treatment led to consistently greater BMI percentage increases for youths than adults-in 15 studies reporting this information.

Conclusion: Available data thus clearly suggest that across the age span, youths are the most sensitive to weight-gain induced by a commonly prescribed second-generation neuroleptic. Although both low age and low baseline BMI predict increased neuroleptic-induced weight gain, age--particularly at the extremes--appears to be a better predictor of RIS-induced weight gain.

Source of Funding: None

Reference: Wetterling T, Murigbrodt HE: Weight gain: side effect of atypical neuroleptics?
J Clin Psychopharmacol 1999; 19:316-32

POSTER NO. 120

METHODS FOR EXAMINING RISK OF DIABETES IN PATIENTS TAKING OLANZAPINE COMPARED TO CONVENTIONAL ANTIPSYCHOTIC MEDICATIONS

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Background: Recent evidence suggests an increased risk of diabetes with some of the newer antipsychotic medications, particularly olanzapine. Many previous studies examined diabetes risk using large administrative datasets with little or no information about pre-olanzapine treatment periods. Given the chronicity of most psychotic illnesses, ignoring the effects of previous treatments may mask effects of new antipsychotic medications. Additionally, few studies have examined the risk of diabetes among patients with concurrent substance use disorders.

Methods: We examined Medicaid reimbursement data for 199 patients receiving treatment for a psychotic illness and substance abuse. 172 of these individuals had filled at least one prescription for an antipsychotic medication during a 10-year period (1991 to 2001). We examined the subset of these individuals (N=147) who had filled a prescription for olanzapine or a conventional antipsychotic medication following the FDA approval of olanzapine. We used survival analyses to examine time-from-starting-medication (olanzapine or conventional) to the first claim for diabetes treatment for various groupings of patients: all patients; all except individuals with evidence of diabetes prior to the FDA approval of olanzapine; all except individuals who had treatment with clozapine; all except individuals who had treatment with any atypical antipsychotic medications other than olanzapine; and the most restrictive criteria which excluded all individuals with evidence of diabetes prior to the FDA approval of olanzapine and/or who had treatment with any atypical antipsychotic medications other than olanzapine.

Results: When all patients were included, those taking olanzapine were no more likely to receive diabetes treatment than those taking conventional antipsychotic medications (Figure 1A). Under the most restrictive exclusion criteria, however, patients taking olanzapine were marginally more likely to receive diabetes treatment than those taking conventional antipsychotic medications (Wilcoxon statistic(1)=3.41, p=.06; Figure 1B; 26% (N=8) versus 4% (N=1)). In addition, the risk of developing diabetes for patients on conventional antipsychotic medications-but not for patients on olanzapine-- increased with lifetime exposure to an atypical, particularly clozapine.

Conclusion: Relative risk of diabetes varies by past treatment history as well as current medication. Analyses which fail to take into account previous treatment history may understate the risk of diabetes associated with olanzapine.

Source of Funding: NIMH grants R01 MH-59312, R01 MH-63463, R01 MH-52872 and R01 MH-52872S; NIAAA grant R01 AA-10265; and SAMHSA grants UD3 SM-51560, UD3 SM-51802, and U1G SM-52096

POSTER NO. 121

THE IMPACT OF CLOZAPINE ON AGGRESSIVE BEHAVIOR AMONG CHILDREN AND ADOLESCENTS WITH SCHIZOPHRENIA

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Objective: The aim of this project was to evaluate the effectiveness of clozapine on aggressive behavior for treatment-refractory adolescents with a DSM-III-R/DSM-IV diagnosis of schizophrenia (295.x) or schizoaffective disorder (295.7) who had been initiated on clozapine therapy between November 1997 to August 2001 at Bronx Children's Psychiatric Hospital (BCPC).

Methods: Using a mirror-image design, the frequency of administration of emergency oral and injectable medications and the frequency of seclusion events 12 weeks prior to and 12 to 24 weeks after clozapine treatment (when optimal clozapine levels were achieved) was compared.

Results: There was a statistically significant decrease in the frequency of administration of oral prn medications for aggression from the pre-clozapine treatment period (up to 3 months prior to clozapine initiation) to the mirror-image clozapine treatment period (3 months to 6 months of clozapine treatment, (.20 (.15) vs. .06 (.1), z = -3.36, p =.001, n =22). Similarly, there was a significant decrease in the frequency of administration of injectable prn medications for aggression from the pre-clozapine treatment period to the mirror image clozapine treatment period, (.06 (.07) vs. .01 (.0), z =-2.69, p =.007, n =11). There was also a significant decrease in the frequency of seclusion events for aggression from the pre-clozapine treatment period to the mirror image clozapine treatment period, (.06 (.07) vs. .01 (.01), z =-2.95, p =.003, n =11).

Conclusion: These preliminary data indicate the benefits of clozapine treatment in adolescents with treatment-refractory schizophrenia for aggressive behaviors. Although, open data limit conclusions from this study, it is important that there was a clinically significant improvement in aggressive behaviors that enabled patients to be discharged to a less restrictive setting. Additional controlled clinical trials of clozapine are needed in treatment-refractory children and adolescents.

Source of Funding: This study was funded by NIMH grants MH-60221 to Dr. John Kane, MH-64556 and a NARSAD award to Dr. Sanjiv Kumra.

POSTER NO. 122

SAFETY PROFILE OF ARIPIPRAZOLE IN PSYCHOSIS OF ALZHEIMER'S DEMENTIA: POOLED ANALYSIS

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Objective: To characterize the safety and tolerability of aripiprazole in elderly patients. Methods: Safety data from two 10-week double-blind placebo-controlled trials in patients with psychosis of AD were pooled (N=458). The dosing regimen of aripiprazole consisted of titration in the 2-15 mg/d range.

Results: Discontinuation rates due to adverse events were 8% with placebo and 12% with aripiprazole. There was no clear pattern of adverse events leading to discontinuation in either group. The most common adverse event reported in both groups was accidental injury: 18% with placebo and 15% with aripiprazole. The only adverse event that occurred in the aripiprazole group at a frequency greater by at least 5% than in the placebo group was somnolence (3% placebo vs 11% aripiprazole). Most cases of somnolence reported with aripiprazole were mild to moderate and only two patients discontinued therapy because of this adverse event. EPS-related adverse events were reported in 4% of patients treated with placebo and 5% of those treated with aripiprazole.

Conclusions: Data from two trials in patients with psychosis of AD indicate that aripiprazole is safe and well tolerated in this patient population, with low rates of EPS and discontinuation due to adverse events.

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Kindermann SS, Dolder CR, Bailey A, Katz IR, Jeste DV: Pharmacological treatment of psychosis and agitation in elderly patients with dementia: four decades of experience. Drugs Aging. 2002;19(4):257-276.

POSTER NO. 123

RELIABILITY ANALYSIS AND CONSTRUCT VALIDITY OF THE CHANGES IN SEXUAL FUNCTIONING QUESTIONNAIRE (CSFQ) SHORT FORM FOR WOMEN AND MEN

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Objective/Background: The CSFQ is a clinical and research instrument with 5 subscales of sexual functioning. It has well-established psychometric properties. It has been translated into a number of languages with reliability and validation studies in Spanish also established. The CSFQ can be used to establish the level of sexual function and to track changes systematically in clinical populations.The objective of the study was to document the internal consistency and factor structure of the CSFQ to assess sexual dysfunction in the 3 phases of the sexual response cycle (i.e., desire, arousal and orgasm).

Methods: Data collected from 6, 268 adult outpatients (72% women) who completed the CSFQ in a multi-site study that included over 1,101 primary care clinics were entered and analyzed using SPSS software. The internal reliability of the CSFQ was investigated by calculating Cronbach's a coefficient, which relies on the average inter-item correlations. A factor analysis (principal component analysis: extraction method using a varimax rotation with kaiser normalization) was conducted to identify the pattern of correlations found in the CSFQ for men and women who were above and below threshold for sexual dysfunction.

Results: Both Cronbach's a and the factor analysis support the validation of the scale structure of the CSFQ that corresponds to the three phases of the sexual response cycle (i.e., desire, arousal and orgasm). Results are presented for males and females above and below the clinically established threshold for sexual dysfunction.

Conclusion: This study further validates the CSFQ as brief, 14-item instrument to evaluate sexual functioning by phases of the sexual response cycle.

Source(s) of Funding: GlaxoSmithKline & Academic Institutional Support

POSTER NO. 124

INCIDENCE OF MORTALITY DURING ANTIPSYCHOTIC CLINICAL TRIALS OF ELDERLY PATIENTS WITH DEMENTIA

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Background: Antipsychotic agents are sometimes prescribed to patients with dementia-related psychosis. These patients may be physically frail due to advanced age and comorbid illness. Deaths have been reported in elderly patients with dementia during clinical trials of several antipsychotic medications.

Methods: Data from seven studies (five double-blind and two open-label) of olanzapine in elderly patients with dementia (Alzheimer's, Vascular, or Mixed) were analyzed to examine mortality. Data from the double-blind placebo-controlled studies (four evaluating dementia-related psychosis and one evaluating dementia-related cognitive symptoms) were integrated for analysis and included 1184 olanzapine- and 478 placebo-treated patients; one study compared olanzapine (n=204) with risperidone (n=196). Mortality was also examined in an open-label study of tardive dyskinesia in olanzapine- (n=149) or conventional antipsychotic-treated patients (n=143). Crude and exposure-adjusted mortality incidences were calculated. Fisher's exact test was used to identify potential baseline and post-randomization mortality risk factors. An overall database (n=1610), including data from a seventh open-label olanzapine-only study (n=81), analyzed overall mortality incidence in patients receiving olanzapine treatment across all seven studies.

Results: In double-blind comparisons, incidence of mortality was significantly greater among olanzapine- than among placebo-treated patients (3.5% vs.1.5%, p=.024), but did not differ significantly between risperidone- and olanzapine-treated patients, nor between conventional antipsychotic- and olanzapine-treated patients. Exposure-adjusted incidence of mortality (per 10 patient-years) was not significantly different between the olanzapine- (1.095; 95% CI=0.789-1.481) and placebo-treated patients (0.477; 95% CI=0.192-0.983). In the olanzapine overall database, exposure-adjusted incidence was 1.444 per 10 patient-years (95% CI=1.141-1.802). Irrespective of treatment group, risk factors for mortality in these placebo-controlled studies included: age >80, lower baseline Mini-Mental State Examination score, benzodiazepine use, weight loss or gain 7%, treatment-emergent sedation, treatment-emergent malnutrition/dehydration, treatment-emergent dysphagia, and treatment-emergent pulmonary conditions. Risk factors associated with a higher incidence of mortality in olanzapine- compared with placebo-treated patients included: age >80, concurrent benzodiazepine use, treatment-emergent sedation, or treatment-emergent pulmonary conditions.

Conclusions: In this analysis of clinical trials of elderly patients with dementia, incidence of mortality was greater among olanzapine- than placebo-treated patients. No significant differences in incidence of mortality were observed between patients treated with olanzapine or risperidone, and olanzapine or conventional antipsychotics. Risk factors associated with mortality were identified. Olanzapine and other antipsychotic agents are not approved for the treatment of dementia in the United States.

These findings should be carefully considered by prescribers electing to treat elderly patients who have dementia-related psychosis with olanzapine or other antipsychotic agents.

Source of Funding: Lilly Research Laboratories

POSTER NO. 125

BIPOLAR DEPRESSION AND UNIPOLAR DEPRESSION RESPONSE TO TREATMENT IN THE CONTEXT OF COMORBID ALCOHOLISM

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Background: Earlier studies using modern research diagnostic criteria observed that depression in bipolar and unipolar disorders were clinically homogeneous and responded equally well to somatic treatments. More recent findings, however, pointed to the different neuroanatomical correlates for bipolar disorder as compared to major depression. Bipolar depression represents a treatment challenge and optimized treatments include the use of mood stabilizers. Furthermore, carefully conducted long-term follow-up studies have demonstrated the predominance of depressive symptoms as the prevalent pathological state in bipolar disorder. Although alcohol dependence is a highly frequent comorbid condition in both bipolar and unipolar depression, limited information is available regarding the course of depressive symptoms in these mood disorders when complicated by alcoholism. The objective of this prospective study is to examine the course and response to treatment of depressive symptoms in a cohort of bipolar alcoholics as compared to the course of depressive symptoms in a cohort of unipolar depressed alcoholics.

Methods: The sample consisted of 2 cohorts of a total of 116 subjects with SCID or PRISM/ DSM-IV diagnoses of bipolar disorder and comorbid alcohol dependence (n=56) or unipolar major depression and comorbid alcohol dependence (n=60). Subjects in both cohorts received optimized treatment for their mood symptoms, which included mood stabilizers for the bipolar alcoholics cohort. Depressive symptoms were measured for 10 consecutive assessments over a 6-month period using the 25-item Hamilton Rating Scale for Depression (HAMD-25). The HAMD-25 consists of the 17-item HAMD + 8 reverse neuro-vegetative symptom items thought to capture relevant aspects of depression in bipolar disorder. We used the mixed model analysis to determine the trajectory of depressive symptoms as measured by the HAMD-25, the HAMD-17, and the reverse neuro-vegetative symptoms subscale. We also controlled for baseline (pretreatment) demographic (age, gender, race, socioeconomic status) and clinical (baseline HAMD-25 and baseline alcohol and other drug use, overall psychiatric severity, and baseline functioning) variables.

Results & Conclusion: The results showed that bipolar alcoholics had slower rate of reduction in depressive symptoms (HAMD-25, HAMD-17, and neuro-vegetative symptoms) than depressed alcoholics. While the mean HAMD-25 score decreased to 12 points by week 10 for the depressed alcoholics cohort, for the bipolar alcoholics cohort it did not reach 12 points score throughout the 6-month study period. Unexpectedly, bipolar alcoholics had lower initial scores on the reverse neuro-vegetative symptoms compared to depressed alcoholics. While male gender (p=0.01) and African Americans (p=0.01) were significantly associated with higher HAMD-25 score in the bipolar sample, there was only a trend for baseline drug use (p=0.08) and overall psychiatric severity (p=0.06) to be significantly associated with higher HAMD-25 score in the unipolar depression group. Although baseline, pretreatment, HAMD-25 was significantly associated with treatment HAMD-25 score of both groups, the strengths of the association were more pronounced with the bipolar alcoholics group. These results point to the persistent nature of depression in bipolar alcoholics and highlight the need for more effective treatment interventions. Both gender and ethnicity may also play an important role in the course of depressive symptoms in bipolar alcoholics.

Source of Funding: This work was supported by USPHS Grants R29AA10523; R01AA11929; R01AA13370, and a VA VISN4 MIRECC grant.

POSTER NO. 126

TC-1734-112 A SELECTIVE NEURONAL NICOTINIC RECEPTOR (NNR) AGONIST IN THE TREATMENT OF COGNITIVE DISORDERS - PHASE 1 RESULTS

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Objective/Background: Neuronal nicotinic agonists are clearly involved in various aspects of cognition including attention, memory and learning both in normals and demented patients. These findings have spurred considerable research efforts to develop ligands selective for CNS NNRs, such as ABT-418 and ABT-089 from Abbott laboratories, SIB-1508Y and SIB-1553 from SIBIA, and GTS-21 from Taiho pharmaceuticals. These molecules have however lacked sufficient selectivity, such that peripheral side effects like nausea/vomiting and cardiovascular changes, have resulted in termination of clinical development. TC-1734 is a selective partial agonist at the CNS alpha4beta2 neuronal nicotinic receptor which does not activate ganglion or muscle-type nicotinic receptor at significantly higher concentrations. This compound is orally active resulting in long-lasting cognitive effects in a variety of animal models and has well demonstrated neuroprotective properties.

Methods: Phase 1 clinical trials have been completed. In a SRD study doses from 2 -320mg were explored in 49 male volunteers. In an MRD study a further 18 male volunteers received 50,100 or 200mg for 10 days.

Results: These studies indicated the drug to be safe and well tolerated. No changes of clinical significance were detected on biochemistry testing, urine analysis, vital signs, ECG and 24 hour Holter monitoring. Adverse events (AEs) were mild-moderate in intensity, resolved without intervention and did not lead to dropout. Non-specific AEs like headache, dizziness and asthenia were reported most frequently. Importantly nausea and vomiting were not seen. Cardiovascular changes were limited to orthostatic events that were usually asymptomatic.PharmacoEEG assessment indicated the drug entered the brain and caused changes of an acceleration type (power shifting from lower to higher frequency bands) - typical of nicotinic stimulation. Results on a cognitive test battery (CDR) found no changes after single doses, but improvement in cognition after 10 days dosing. These changes included improvement in immediate/delayed word recall and power of attention.

Conclusion: TC-1734 is the most advanced selective CNS neuronal nicotinic agonist to move into full-scale clinical development. These Phase 1 results confirm that this compound does not cause the peripheral side effects characteristic of earlier molecules. Importantly TC-1734 seems also to have the potential for a beneficial effect in cognitive disorders.

Source(s) of Funding: Targacept Inc

POSTER NO. 127

SUBSTANCE USE COMORBIDITY IN MAJOR DEPRESSION: STAR*D PRELIMINARY FINDINGS

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Objective/Background: Patients with major depressive disorder (MDD) often present with concurrent substance use disorders (SUDs) involving alcohol and/or illicit drugs. This analysis compares the depressive symptomatic presentation and a range of clinical and demographic features of patients with MDD and concurrent SUDs versus those without an SUD, in order to clarify the clinical and demographic differences between groups and how concurrent SUDs may alter the clinical presentation of MDD.

Methods: The first 1500 outpatients with nonpsychotic MDD enrolled in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study were divided into those with and without concurrent SUD symptoms as ascertained by a self-report instrument, the Psychiatric Diagnostic Screening Questionnaire. These groups were then compared.

Results: Altogether, 28% (n=418) were found to have SUD symptoms. These patients were more likely to be male ($p<0.0001$), to be either divorced or never married ($p=0.018$), to have a younger age of onset of depression ($p=0.015$), and to have a higher rate of previous suicide attempts ($p=0.012$) than those without SUD symptoms. The presence of SUD symptoms did not alter the overall depressive symptom pattern of presentation, except that the dual-diagnosed patients had higher levels of hypersomnia ($p=0.007$) and suicidal ideation ($p=0.043$) compared to those without SUD symptoms.

Conclusion: Depressed patients with concurrent SUD symptoms are disproportionately younger, single or divorced, and male. These patients' depressive illness begins at an earlier age and they are more likely to have made prior suicide attempts. The presence of an SUD seems not to affect the overall symptomatic presentation of major depression, though those with such a comordity are more likely to report hypersomnia and suicidal ideation.

Source(s) of Funding: NIMH

POSTER NO. 128

ANTIDEPRESSANT EXPOSURE MAY PROTECT AGAINST DECREMENT IN FRONTAL GRAY MATTER VOLUMES IN GERIATRIC DEPRESSION

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Objective/Background: Depressed elderly patients with and without antidepressant exposure were compared to normal controls to examine the effects of prior antidepressant exposure on the MRI regional brain volumes.

Methods: Patients and controls were closely matched by age and education. They underwent thorough neuropsychiatric, laboratory, and physical examinations and the MRI scans. Measures of the total frontal lobe and the frontal gray and white matter volumes corrected by the intracranial volume were obtained using magnetic resonance imaging (MRI), together with clinical measures of medical (CIRS) and cerebrovascular burden (CVRF). A thorough information about prior exposure to antidepressant drugs was collected using multiple information sources. The groups were compared using univariate and multivariate analyses of covariance, controlling for age.

Results: The study sample was comprised of 41 patients with MDD (32 women, 11 antidepressant exposure and 30 drug-naive; mean age 70.5 + 7.6) and 41 controls (20 women; mean age 72.2 + 7.3). In the univariate analysis, the depressed group had lower MMSE scores ($p<0.001$); greater severity of medical comorbidity (CIRS scores) ($p<0.002$) compared to the controls. The depressed group had smaller total corrected orbito-frontal ($p<0.001$), gray ($p<002$) and white matter ($p<0.02$) volumes than the controls. In the multivariate analysis, controlling for age, the depressed group had smaller corrected frontal lobe volumes, total right and left, and or bito-frontal volume, total and gray matter volume compared to the controls. Depressed patients with prior antidepressant exposure had larger frontal and OFC gray matter volumes compared to drug-naive depressed patients, but smaller than corresponding volumes of normal controls.

Conclusion: We observed the groups differences in frontal regional brain volumes with depressed elderly patients having smaller OFC gray matter volumes than normal controls. Antidepressant exposure may protect against gray matter loss in geriatric depression.

Source(s) of Funding: This work was supported in part by the K23-MH01948 and the NARSAD Young Investigator Award to Dr. Lavretsky and grants MH55115, MH 61567 & KO2-MH02043 (AK)

POSTER NO. 129

EXTENDED USE OF NICOTINE REPLACEMENT THERAPY TO ACHIEVE SMOKING CESSATION IN PERSONS WITH SCHIZOPHRENIA

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Objective/Background: Persons with schizophrenia have an exceptionally high prevalence of tobacco use, 80 â " 90 %. The use of tobacco by this population may be a form of self-medication related to the biology, therapy and symptoms of schizophrenia. Thus long-term use of nicotine replacement therapy (NRT) may be useful in helping this population reduce or quit tobacco use.

Methods: Fifty smokers with a diagnosis of schizophrenia or schizo-affective disorder enrolled in a 9-month program providing group support and NRT (patches) in individually adjusted doses set to maintain baseline nicotine intake. Smoking history, saliva cotinine levels and Fagerstrom scores were recorded at baseline. All participants attended weekly group support/motivation sessions. Smoking activity was determined by measuring CO levels in expired air. Efficacy of long-term NRT was determined by comparing relapse rates on placebo vs. active patches during the final 6 months.

Results: The average Fagerstrom nicotine addiction score was 7.4, approximately twice that reported for normal populations; scores were rated high or very high by 85% of the subjects. Nevertheless, sixty days into the open label phase, 66% of the subjects had reduced their use of tobacco by at least 75%. After ninety days of open label treatment, eighteen subjects (36%) were smoke-free and qualified to enter the six-month, single blind phase, 8 on placebo and 9 on active patch (1 subject quit smoking and the use of the patch prior to ninety days). A significantly greater proportion of those on placebo (8 of 8) than those on active patches (3 out of 9) relapsed prior to completion of the 6-month period. This difference is statistically significant, chi-square = 8.24, df = 1, p = .004.

Conclusion: Results of this study indicate that persons with schizophrenia experience a high level of nicotine addiction but a significant number wish to quit tobacco use and are successful. Long term use of NRT appears to be important for sustained success. Additional studies are required to better define the parameters and utility of long term NRT in this population.

Source(s) of Funding: American Legacy Foundation and Via Christi Foundation. Placebo patches donated by GlaxoSmithKline.

POSTER NO. 130

GALANTAMINE IN THE TREATMENT OF DEMENTIA IN HISPANIC PATIENTS:AN EFFECTIVENESS MULTICENTER OPEN LABEL STUDY

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Objective/Background: The objective of the study was to start to evaluate the effectiveness and safety of galantamine in a community sample of Hispanic demented subjects.

Methods: Subjects: 104 demented patients (Alzheimer's 53, Vascular dementia 23, and mixed dementia 28) were treated for 3 months with an escalating monthly dose of galantamine that started with 8mg daily and finished at the third month with 24-mg. a day. The outcome measures were the difference in Mini-Mental Status Exam (MMSE) score at baseline and end point, an adapted version of the Clinical Global Impression of Change scale (CGIC), spontaneously reported adverse events and an adapted CGIC to evaluate tolerability.

Results: Subjects showed statistically significant differences ($p< 0.001$, student t test) in MMSE showing improvements ranging from -2. to -5 points from baseline. Most physicians found patients in the AD and in the vascular dementia groups to be very much improved or improved. Most subjects in the mixed type dementia group were either improved or unchanged. The difference between the AD group and the mixed type group were statistically significant ($p= 0.001$). The safety profile was benign with only gastrointestinal symptoms observed in more than 5% of the study subjects. No deaths and only one serious adverse event were reported.

Conclusion: To our knowledge this is the first multicenter effectiveness study evaluating a cholinesterase inhibitor in Hispanic demented outpatients. This study demonstrates the feasibility of performing clinical trials in this population.

Source(s) of Funding: Jansen Cilag Mexico and Medical University of South Carolina

POSTER NO. 131

ETHNIC VARIATIONS IN ANTIDEPRESSANT RESPONSE RATE IN SUBJECTS WITH MAJOR DEPRESSION AND CO-OCCURRING ALCOHOL USE DISORDER: THE ROLE OF SEROTONIN TRANSPORTER POLYMORPHISM

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Objective: An estimated 9.4 and 14% of the population will develop alcohol abuse or dependence in their lifetime, of these, 13.8% describe their current alcohol use disorder as secondary to a major depressive disorder; conversely approximately 30% of those with depression will develop a diagnosis of alcoholism. The high incidence of comorbidity has lead to the theory that there is a common underlying biological mechanism for both disorders. Family studies and post mortem measurements of 5-HIAA in CSF and serotonin transporter binding indicate disruptions in serotonergic functioning are common to both depression, suicide and alcoholism and may represent an underlying pathological state. The present study investigates the efficacy of the SSRI citalopram, in reducing problem drinking and depression in Caucasian and African American subjects with major depression and co-occurring alcohol use disorder. We investigate the role of the 5-HTTLPR and CYP2C19 genetic polymorphism in predicting treatment response. Our primary hypothesis is that African American subjects will demonstrate a more robust antidepressant response and a greater decrease in weekly alcohol intake at lower doses of citalopram due to differences in the frequency of these allelic variants. Positive anti-depressant response and decreased alcohol intake will be associated with the presence of the 5-HTTLPR ll polymorphism. Our secondary hypothesis is that both African Americans and Caucasians will show improvement in depressive measures and reduced alcohol intake with citalopram treatment.

Methods: This is an 8-week pilot study of open label, once daily flexible dose citalopram (20-60mg) in n= 20 subjects (10 African American and 10 Caucasians) meeting criteria for DSM-IV Major Depression and Alcohol abuse or dependence. After a one week placebo washout period subjects were evaluated weekly by a study coordinator and physician using the BDI, HAM-D, CGI, and Time Line Follow Back (TLFB) self-report of weekly alcohol intake. Abstinence from alcohol was not required in this study and subjects were allowed to participate in Alcoholics Anonymous but regular psychotherapy sessions were exclusionary. Routine laboratory evaluation, including testing of liver enzymes and urine drug screen was performed on all subjects in addition to weekly Breathalyzer testing.

Results: Subjects are actively enrolled and in recruitment and preliminary data from 8 subjects is presented. Of these 8 subjects, a subgroup of 6 actively drinking subjects TLFB data was analyzed, 5 Caucasian and 1 African American. Subjects in this subgroup decreased the average number of drinks per week from a baseline measurement of 20.6 drinks per week to a week 8 study completion average of 10.8 drinks. Four of these 6 subjects showed a definite decrease in alcohol intake at week 8, one subject was unchanged within 1 drink (averaged baseline range to week 8 documented alcohol consumption) and one subject increased consumption from 12 to 16 drinks weekly. This African American subject had a decrease in his HAM-D score from 21 to 16 at study completion. The HAM-D scores in this subgroup of 6 decreased from an average of 25.5 at baseline to 20.6 at study completion week 8. When the 2 remaining study completers for whom TLFB data are not available are included in this analysis the HAM-D average score for all 8 subjects decreased from a baseline of 24.4 to a week 8 average HAM-D of 16. Among the 4 of 6 subjects who reduced alcohol intake by study completion, 3 of 3 who had TLFB data available from week 2 showed a positive response at week 2. Genotype analysis of these 8 study completers is not yet available at the time of this presentation.

Conclusions: Treatment with citalopram reduced symptoms of depression and alcohol intake with benefits seen as early as week 2. In 6 of 8 subjects there was an improvement in HAM-D scores by study completion. All but one of the subjects had a corresponding decrease in weekly alcohol consumption by study completion. The increase in alcohol intake in the single African American subject does not support our hypothesis that African Americans subjects will show greater improvement in depressive symptoms and a larger reduction in alcohol intake with citalopram. This subject is, to date our only African American subject and it is not possible to generalize this finding definitively. Interestingly, though this African American subject did not have a reduction in alcohol intake he did have a modest decrease in Ham-D score. Further analysis and data collection is needed pending final recruitment of our target N=20.

Disclosure/Source of Funding: Departmental Funds, American Psychiatric Association/Substance Abuse Mental Health Services Administration Minority Fellowship Award

POSTER NO. 132

ENHANCED DELAYED RECALL OF PRE-DRUG WORD LIST FOLLOWING ACUTE LORAZEPAM AND TRIHEXYPHENIDYL ADMINISTRATION IN HEALTHY ELDERLY

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Objective/Background: Benzodiazepines (BZPs) have been shown to impair recall of information presented after acute drug administration, whereas delayed recall of pre-drug word lists has been reported to be enhanced relative to placebo. The underlying neurobiological mechanism for this memory enhancement is poorly understood, but has been ascribed to less retroactive interference due to BZP-induced anterograde impairments. Centrally active anticholinergic agents also produce anterograde amnestic effects, however it is not known if they also enhance delayed recall of pre-drug word list and if the magnitude of this effect is similar to that of BZPs. These considerations prompted us to compare the effects of acute doses of lorazepam and trihexyphenidyl on delayed recall of pre- and post-drug word lists in a group of healthy elderly who received both of these medications.

Methods: Twenty-four cognitively intact elderly (60+ years of age) participated in 2 different double-blind placebo-controlled cross-over studies examining the cognitive effects of acute oral doses of lorazepam (0.5 mg and 1 mg) and trihexyphenidyl (1 mg and 2 mg), each dose administered on separate days at least 1 week apart. Total and delayed recall for each session was assessed using the Buschke Selective Reminding Task (BSRT) administered pre-drug and at 1, 2.5, and 5 hours post-drug. At the end of the 5th hour testing session, delayed recall of the 4 word lists presented on that day was determined.

Results: Single acute doses of lorazepam (0.5 and 1 mg) resulted in significant impairments in delayed and total recall. Trihexyphenidyl (2 mg) also impaired delayed and total recall, however lorazepam (1 mg) resulted in greater impairments. Delayed recall of pre-drug word lists was similarly enhanced by lorazepam and trihexyphenidyl.

Conclusion: Similar enhancement of recall of pre-drug information by lorazepam and trihexyphenidyl was found despite greater anterograde amnestic effects of lorazepam, suggesting that the retrograde facilitation, which we observed, may not be solely due to reduced interference.

Source(s) of Funding: This study was funded, in part, by NIMH Grant MH-56994.

POSTER NO. 133

SMOKING REDUCTION IMPACT ON CYP1A2 ACTIVITY IN A GROUP OF PATIENTS RECEIVING ANTIPSYCHOTICS

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Objective/Background: We hypothesized: 1) Smoke cessation/reduction will be associated with a significant decrease in the activity of CYP1A2. 2) Smoke cessation/reduction will be associated with a significant increase in the steady-state concentration of the neuroleptics metabolized by CYP1A2 received by the patients.

Methods: Eighteen- to 60-year-old male/female smokers (10--40 cigarettes per day) receiving antipsychotic therapy were randomized to one of two study groups: (a) usual dose (21 mg) and (b)high dose patches (42 mg). Treatments were divided into 4 steps, with Step 1 lasting six weeks, and Steps 2-4 lasting two weeks each. Both groups received two identical patches during Steps 1-3, and then tapered to one patch in Step 4. Active nicotine patch treatment was tapered at each new step. Subjects were seen weekly for the first 12 weeks, and then again at Week 24. At Screen, and Weeks 2, 4, 6, 8 and 24, the subjects were given a 100 mg tablet of caffeine and urine was collected for 8-hours. HPLC was utilized to determine the molar ratio (MR) of caffeine metabolites in urine [(AFMU+1U+1X)/17U] to establish their CYP1A2 activity. Antipsychotic levels were obtained concurrently with urine phenotyping.

Results: Fifteen smokers participated in the study. Smoking reduction and cessation was correlated with significant lower MR in urine compared to baseline,($P<0.015$)and ($P<0.05$) respectively. CYP1A2 antipsychotic (haloperidol, fluphenazine, olanzapine, and thiothixine) serum levels increased compared to non CYP1A2 antipsychotics.

Conclusion: Cigarette smoking may be a factor influencing the plasma levels of antipsychotics that are metabolized by CYP1A2. Clinicians should weight the possibility that smoking and the subsequent modulation of antipsychotic metabolism may be the main reason of treatment resistance. Furthermore, reduction or cessation of smoking in patients with schizophrenia may result in need for lower dosages and improved therapeutic effect.

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POSTER NO. 134

MEASUREMENT OF OLFACTORY ABILITY: ODOR IDENTIFICATION IS NOT EQUIVALENT TO OLFACTORY THRESHOLD

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There is a substantial Alzheimer's Dementia literature based upon olfaction as a predictor or as a concomitant of progressive cognitive loss. Most studies have utilized the University of Pennsylvania Identification Test (UPSIT) score as independent variable. UPSIT requires intact cognition and even most normal individuals find suprathreshold odor identification challenging.

If the UPSIT functions is anything more than another cognitive test as some workers have claimed, then measurement of olfactory threshold should lead to improved correlation with other indices of dementia including losses of central cholinergic function and its response to cholinergic pharmacotherapy with modern agents.

Ninety-six volunteer normal subjects performed the UPSIT and underwent measurement of olfaction threshold for odorants n-butanol, phenyethyl alcohol and vanillin in water solution using a forced-choice ascending concentration stepwise method. Results show olfactory threshold increasing as a linear function of age and UPSIT scores decreasing with age in a complex non-linear fashion. UPSIT scores and olfactory threshold for n-butanol are correlated $r = .44$ ($p<.05$) and upon further analysis the relationship is also non-linear. The suprathreshold UPSIT and olfactory threshold measurements are not equivalent and do not measure the same biological parameters. In a study of responsiveness to centrally-active cholinergic agents, the olfactory threshold less burdened with cognitive complexity might be expected to be the better measure.

POSTER NO. 135

LONG-TERM SAFETY AND ADVERSE EVENTS OF RISPERIDONE IN CHILDREN, ADOLESCENTS AND ADULTS WITH MR/DD

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Objective/Background: To examine long-term safety and adverse events (AE's) of risperidone treatment in a sample of children, adolescents, and adults (n = 20) with developmental disabilities (mean treatment duration = 184.2 weeks), following a 46-week prospective risperidone crossover study.

Methods: Twenty children, adolescents, and adults who completed our 46-week prospective crossover study of risperidone and placebo and continued to follow-up in our clinic were examined prospectively for AE's. Dystonias, EPS, akathisia, and tardive dyskinesia were examined clinically and using the Dyskinesia Identification Systems Condensed User Scale (DISCUS) and the Neuroleptic Side Effects Checklist (NSEC). Weight gain and metabolic side effects were also evaluated. We examined another subgroup (n = 9) choosing not to continue on risperidone for withdrawal dyskinesias.

Results: Of 20 patients, one adolescent male, now aged 16 years, has possible early tardive dyskinesia after 318 weeks of risperidone treatment. Two adult females had akathisia (pacing, leg-tapping). One male, aged 27 years, developed oculogyric crisis. Another adolescent male has moderate tremor but also receives seizure treatment with divalproex. DISCUS scores increased in only 2 of 20 patients (10%), by +1 and +4 respectively (possible range 0-60). NSEC scores increased in 4 of 20 patients (20%) (possible range 0-29), by +1 in 2 patients and +2 in 2 patients. All children and adolescents (n = 11) but one, continued to gain significant weight through follow up period (mean = 19.3kg). One patient (20yr) gaining no further weight, received dietary control and topiramate, with weight loss of 1.4kg. Adults (n = 8) showed less weight gain: 4 gained 1.4 to 6.0kg, while 4 lost 0.5 to 3.9kg. Two adult females, one Caucasian and one African American, developed insulin-dependent diabetes mellitus (IDDM), one of whom is in renal failure. Of 9 patients discontinuing risperidone, only one female, aged 13 years, developed withdrawal dyskinesia in the form of transient facial grimacing.

Conclusion: This prospectively examined sample shows a low rate of movement side-effects after a mean of 184.2 weeks of treatment. Children and adolescents continued to gain significant weight, whereas a lesser weight gain and some weight loss occurred in adults. Two adult females developed IDDM, one of whom is in renal failure. Studies of weight control strategies in conjunction with risperidone treatment are urgently needed.

Source(s) of Funding: Abbott Pharmaceuticals, $5,000 unrestricted grant.

POSTER NO. 136

MEMANTINE MONOTHERAPY IS EFFECTIVE AND SAFE FOR THE TREATMENT OF MILD TO MODERATE ALZHEIMER'S DISEASE: A RANDOMIZED CONTROLLED TRIAL

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Objective/Background: Memantine is a low-moderate affinity, uncompetitive NMDA receptor antagonist approved for the treatment of moderate to severe Alzheimer's disease (AD). No well-controlled trials addressing memantine monotherapy in patients with mild AD have previously been performed. Thus, a 24-week, randomized, double-blind, parallel-arm, placebo-controlled Phase III trial was conducted in the U.S. to study the efficacy and safety of memantine in patients with mild to moderate AD.

Methods: Outpatients $\geq$ 50 years with diagnostic evidence of probable AD (NINCDS-ADRDA criteria), an MRI or CT scan consistent with probable AD, and a MMSE score of 10-22 at screening and baseline were enrolled. Patients who met inclusion criteria were randomized to placebo or memantine 20 mg/day (10 mg b.i.d.). Primary outcome assessments were the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog), a measure of cognition, and the Clinician's Interview Based Impression of Change - Plus (CIBIC-Plus), a measure of global status. Both primary endpoint measurements were analyzed using the Last Observation Carried Forward approach (LOCF), and the safety assessment was based on adverse events (AEs), clinical laboratory evaluations, ECGs, and vital signs.

Results: Of 403 patients randomized and treated with memantine (n=202) or placebo (n=201), 82.1% of memantine-treated patients and 82.7% of placebo-treated patients completed the trial. Memantine-treated patients performed significantly better than placebo-treated patients on both primary outcome measures: the ADAS-cog (p=0.003) and the CIBIC-Plus (p=0.004). Memantine was safe and well tolerated and the incidence of AEs was similar for the memantine- and placebo-treated groups.

Conclusion: These results demonstrate that memantine is effective and safe for patients with mild to moderate AD. Taking previously published data into consideration, memantine is efficacious in providing cognitive and global benefit for patients at all stages of AD.

Source(s) of Funding: Forest Laboratories, Inc.

POSTER NO. 137

MEMANTINE IS SAFE FOR SHORT- AND LONG-TERM TREATMENT OF DEMENTIA

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Objective/Background: Memantine, a low-moderate affinity, uncompetitive NMDA receptor antagonist, was approved in the U.S. for the treatment of moderate to severe Alzheimer's disease (AD) in October 2003. Short- and long-term safety and tolerability of memantine for the treatment of dementia were assessed through five double-blind, placebo-controlled trials and four open-label extension studies.

Methods: The short-term safety of memantine in moderate to severe AD patients (n=734; memantine 10-20 mg/day; 12-28 weeks) was assessed in three of the five double-blind, placebo-controlled trials. Two other double-blind trials examined 900 mild to moderate vascular dementia (VaD) patients administered 20 mg/day memantine or placebo for 28 weeks. Long-term safety was assessed by pooling data from four open-label extension studies. AD and VaD patients (n=856) were administered 10-20 mg/day memantine (12-104 weeks). Safety parameters included adverse events (AEs), vital signs and clinical laboratory tests.

Results: In the evaluation of short-term safety, only headache and confusion were reported in $\geq$5% of moderate to severe memantine-treated AD patients at an incidence of at least twice that of placebo. Only constipation was reported in $\geq$5% of memantine-treated VaD patients at an incidence of at least twice that of placebo. In the evaluation of long-term safety, AEs reported by $\geq$5% of memantine patients were agitation, urinary tract infection, fall, accidental injury (causality not indicated) and dizziness (all $\leq$7%). The majority of AEs reported in all studies were considered mild or moderate in severity and not related to memantine. No clinically relevant differences between memantine and placebo patients in the vital signs or laboratory values were observed.

Conclusion: The short- and long-term treatment of dementia with memantine is safe and well tolerated.

Source(s) of Funding: Forest Laboratories, Inc. and Merz Pharmaceuticals GmbH

POSTER NO. 138

THE INFLUENCE OF ETHNIC BACKGROUND AND CARDIOVASCULAR RISK FACTORS ON COGNITIVE DECLINE. ASSESSMENT OF A LONGITUDINAL COMMUNITY BASED SAMPLE

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Objective/Background: 1. To evaluate and compare the influence of gender and ethnicity on the level of cognitive function observed in the Charleston Heart Study (CHS) participants 2. To assess the effects of cardiovascular risk factors on cognitive change in CHS participants

Methods: The CHS is a population-based random sample of African Americans and White Charleston County residents. The subjects were initially recruited in 1960. Subjects were 35 years or older. 2181 subjects were recruited. 787 subjects were African Americans. In 1963, 102 high socioeconomic African-American males were added to the study sample. Cognitive functions were measured in 1987 and 1991. The cognitive battery consisted of : The Portable Mental Status Questionnaire (Pfeiffer), and the Russell's Revision of the Wechsler Memory Scale which includes measurements of Immediate verbal memory, Delayed verbal memory, Immediate visual memory, and Delayed visual memory.

Results:

- Whites Caucasians - Weak association between history of CAD and decline in immediate visual memory (O.R. 1.7 CI 1.0 to 2.8) - Weak association between history of CAD and degree of decline in immediate visual recall (p=.1) and delayed visual recall (p=.055)
- African-Americans - African Americans show higher incidence of cognitive decline even when the analysis took in consideration socioeconomic and other risk factors - Association between history of CAD and decline in immediate visual memory (O.R. 2.6 CI 1.2 to 5.7) - Association between higher BMI and decline in delayed verbal memory (p=.02) - CAD (p=.001) and hypertension (p=.05) were associated with degree of decline in immediate visual memory - History of CAD (p=.02) and higher total cholesterol (p=.006) were associated with the degree of decline in delayed visual memory

Conclusion:

- African American Background increases the risk for cognitive decline even when socioeconomic variables are taken into account. Cardiovascular risk factors appear to influence the pattern of cognitive decline seen with aging
- The profile of cardiovascular factors influencing cognitive decline may be different for whites and African-Americans
- Cardiovascular risk factors may play a greater role in cognitive decline in African-Americans than in whites

Source(s) of Funding: Medical University of South Carolina R03 AG021162

POSTER NO. 139

NEUROPROTECTIVE PROPERTIES OF QUETIAPINE: A POSSIBLE MECHANISM IN TREATMENT OF PSYCHOSIS?

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Objective/Background: Psychosis and agitation are non-specific syndromes associated with schizophrenia, bipolar disorder, dementias and other psychiatric conditions. Etiopathogenesis of psychosis is not clearly understood but recent evidence suggests that regulation of nerve cell loss and survival could play a role. Thus, nerve cell loss has been implicated in early onset schizophrenia (Thompson et al. 2001) and epidemiological studies support the idea that schizophrenia severity may be associated with nerve cell susceptibility to injury (Seeman, 1997). It is further supported by findings of hippocampal volume reduction (Velakoulis et al., 2000) on MRI of the brain in schizophrenia patients (Lieberman et al., 2001). Several studies suggest that certain antipsychotics and mood stabilizers (e.g. valproate) could be neuroprotective (Loy and Tariot, 2002). To further understand the mechanism of antipsychotic drug action, we examined neuroprotective properties of the novel antipsychotic quetiapine used for treatment of psychosis in schizophrenia, bipolar disorder and dementia.

Methods: We treated organotypic hippocampal cultures prepared from 7- to 12-day-old Wistar rats with quetiapine (1 nM to 100 μM). After 2 weeks in culture, slices were exposed to 50 μM N-methyl-D-aspartate (NMDA) for 30 minutes or to oxygen-glucose deprivation (OGD) for 60 to 120 minutes to induce cell death, measured as propidium iodide uptake. Quetiapine was added (1) one day or one week before NMDA, during NMDA, and through a 3-day post-NMDA period; (2) 2 hours before, during, and after NMDA/OGD; (3) during NMDA/OGD exposure; (4) after NMDA/OGD. NMDA antagonist MK801 was used for comparison and added instead of quetiapine in NMDA experiments 3 and 4. One way ANOVA with Bonferroni correction for multiple comparisons was used to determine statistical significance.

Results: Prolonged (1-7 days, experiment 1) but not 2-hour (experiment 2) treatment with quetiapine dose-dependently (1-100 nM) decreased NMDA-induced cell death ($P<0.05$). Unlike the NMDA antagonist MK801, quetiapine was ineffective if applied together with NMDA (experiment 3) and was ineffective after NMDA (experiment 4). In the OGD experiments, quetiapine 10 nM decreased cell death in experiment 3 ($P<0.05$).

Conclusion: Quetiapine decreased NMDA-dependent nerve-cell death in a concentration-dependent manner after exposure for at least 24 hours. Unlike MK801 quetiapine does not appear to block NMDA receptors directly. The neuroprotective action of quetiapine may contribute to its clinical efficacy in treating psychoses of dementia and should be investigated in clinical trials.

Funding Source: The research presented was supported by an investigator-initiated research grant from AstraZeneca Pharmaceuticals LP to AB.

POSTER NO. 140

EFFECTS OF GALANTAMINE AND DONEPEZIL ON ATTENTION IN PATIENTS WITH MODERATE-TO-SEVERE ALZHEIMER'S DISEASE

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Objective/Background: Galantamine, unlike other members of the acetylcholinesterase inhibitor (AChEI) class, has a dual mechanism of action as an allosteric modulator of nicotinic cholinergic receptors. Nicotinic acetylcholine receptors (nAChR) are involved in cognitive functions, including attention, learning, and memory. Several studies suggest that stimulation of nAChRs can improve attentional capacity in patients with AD. Therefore, a pilot study was conducted to compare the effects of galantamine and donepezil on functional abilities, attention, cognition, and behavioral disturbances in patients with moderate-to-severe Alzheimer's disease (AD).

Methods: In this 1-year comparative study, 182 patients were randomized to receive galantamine (N=94; doses escalated to an optional maximum of 24 mg/day at Week 13) or donepezil (N=88; optional maximum: 10 mg/day at Week 4). The Cognitive Drug Research Computerized Assessment System for Demented Patients (CDR) was administered to a subset of patients (n=80). Tasks from the CDR included 3 measures of attention (simple reaction time, digit vigilance, and choice reaction time), plus a measure of episodic long-term memory (picture recognition).

Results: Galantamine-treated patients (n=41) demonstrated improvements from baseline in all 3 CDR attentional tasks during the first 6 months (simple reaction time, P=0.0299 at Week 26; choice reaction time, P=0.0015 at Week 6), with no significant declines from baseline at 1 year. In contrast, donepezil-treated patients (n=39) either failed to improve or, in the case of digit vigilance, significantly declined from baseline (P=0.0131 at Week 52). Significant differences between galantamine and donepezil were noted at Week 6 for digit vigilance (P=0.0313) and choice reaction time (P=0.0301), as well as for composite measures (combined reaction time scores, P=0.0276 at Week 6).

Conclusion: In this first long-term head-to-head comparison of galantamine and donepezil, galantamine demonstrated more favorable effects on attention, possibly as a result of its ability to allosterically modulate nicotinic receptors.

Source(s) of Funding: Janssen

POSTER NO. 141

FUNCTIONAL AND BEHAVIORAL EFFECTS OF MEMANTINE IN ALZHEIMER'S DISEASE

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Objective/Background: Alzheimer's disease (AD) is a progressive, neurodegenerative illness associated with cognitive deficits, functional decline and behavioral disturbances. Memantine, a low-moderate affinity, uncompetitive NMDA receptor antagonist, is thought to allow normal physiological activation while blocking prolonged pathological activation of the NMDA receptor, one factor implicated in the pathology of AD. Memantine was approved in the U.S. for the treatment of moderate to severe AD based on demonstrated efficacy in cognition, function and global status in two trials, one of which included patients treated with ongoing donepezil therapy. This report provides additional analyses of the functional and behavioral effects of memantine in moderate to severe AD patients stabilized on donepezil.

Methods: A 24-week double-blind, placebo-controlled trial was conducted in moderate to severe AD patients treated with ongoing donepezil therapy (N=404) and randomized to memantine or placebo. Functional abilities were assessed using the modified Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale ADCS-ADL_{19} and the Behavioral Rating Scale for Geriatric Patients (BGP) Care Dependency subscale. The ADCS-ADL_{19} was administered at baseline, Weeks 4, 8, 12, 18 and 24; the BGP Care Dependency subscale was administered at baseline and Week 24. Behavioral symptoms were assessed using the Neuropsychiatric Inventory (NPI), administered at baseline, Week 12 and the final visit. The efficacy analyses were based on the ITT population, using both OC and LOCF approaches.

Results: Memantine-treated patients demonstrated significantly greater functional ability on both the ADCS-ADL^{19} and the BGP Care Dependency scales compared to placebo-treated patients (p=0.028, p=0.001, respectively). An item analysis of the ADCS-ADL_{19} revealed that at Week 24, abilities in grooming, being left alone, and watching television were statistically significant in favor of memantine. NPI total score favored memantine treatment over placebo (p=0.002). At Week 24, NPI domains demonstrating statistically significant treatment differences in favor of memantine were agitation/aggression, irritability/lability, and appetite/eating.

Conclusion: Memantine treatment in patients receiving stable treatment with donepezil is associated with less functional and behavioral deterioration in AD than with donepezil treatment alone.

Source(s) of Funding: Forest Laboratories, Inc.

POSTER NO. 142

A DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL OF C-1073 (MIFEPRISTONE) IN THE TREATMENT OF PSYCHOTIC MAJOR DEPRESSION

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Background: Psychotic depression is characterized by abnormalities in hypothalamic pituitary adrenal (HPA) axis activity. In a previous trial double-blind trial, C-1073 (mifepristone), a selective glucocorticoid receptor antagonist, had therapeutic benefits when added to standard pharmacotherapy for psychotic depression. In this trial the efficacy of C-1073 is compared with that of placebo in patients who are not on standard pharmacotherapy for the first 7 days.

Methods: Patients who met DSM-IV criteria for PMD and were not on either antidepressants or antipsychotics were randomized in a 1:1 ratio to receive adjunctive C-1073 or placebo for 7 days in an in-patient setting. Patients were followed for a total of 28 days. The study was powered to demonstrate a 30% reduction in the total Brief Psychiatric Rating Scale (BPRS) at both days 7 and 28. Secondary measures included a 50% reduction at days 7 and 28 in (BPRS) positive symptom subscale, the Hamilton depression Rating Scale, and the Montgomery Asberg Depression Rating Scale.

Results: 221 patients were randomized and patients in both the C-1073 and control groups improved significantly from baseline. Patients on C-1073 were significantly more likely to achieve a 30% improvement at days 7 and 28 than were placebo treated patients. In addition, C-1073 treated patients were significantly more likely to achieve a 50% reduction in days 7 and 28 on the BPRS positive symptom subscale. There were no significant benefits on the depression rating scales. C-1073 appeared well tolerated for the duration of the study with no AEs statistically more common in the C-1073 than placebo group.

Conclusion: A 7-day course C-1073 appears to rapidly and significantly effect psychotic symptoms in psychotic major depression. In addition, the effects of the drug appear to be sustained for at least 3 weeks after the drug is stopped. This study provides additional evidence that the specific glucocorticoid receptor antagonist, C-1073, may have a role in the treatment of psychotic depression.

Source(s) of Funding: Corcept Therapeutics

POSTER NO. 143

MEMANTINE PREVENTS Aß$_{1-40}$-INDUCED APOPTOTIC CELL DEATH IN THE RAT HIPPOCAMPUS

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Objective/Background: Injections of the ß-amyloid peptide (Aß1-40) in rat hippocampus have been shown to produce lesions in the dentate gyrus and CA1 area of the hippocampus. In this model of Aß$_{1-40}$ hippocampal toxicity, the uncompetititive NMDA receptor antagonist, memantine, reduces the extent of Aß$_{1-40}$-induced lesions in the hippocampus.

Methods: In Alzheimer's disease (AD), neurons in the hippocampus and entorhinal cortex exhibit nuclear DNA fragmentation indicating apoptosis and neuronal vulnerability to insult. Apoptosis can be regulated by the B-cell leukemia-2 gene product (Bcl-2) family (e.g., Bcl-2, Bcl-x, Bax, Bak and Bad proteins) with apoptosis being prevented by Bcl-2 and Bcl-x, and promoted by Bax, Bak and Bad. In AD, several neurons exhibiting DNA damage also show increased Bcl-2 immunoreactivity. This increase in Bcl-2 expression in AD occurs in parallel with increasing disease severity and is seen predominantly in neurons that do not contain neurofibrillary tangles. Therefore, it is likely that increased levels of Bcl-2 in AD is a response by healthy, non-tangle bearing neurons to a deleterious brain environment. In the present study, we determined whether the neuroprotective effects of memantine in rats injected with Aß$_{1-40}$ in hippocampus are mediated by modulation of Bax, Bad or Bcl-2. DNA-fragmentation was determined by TUNEL staining and Bax-, Bad- and Bcl-2-immunoreactivity was determined by immunohistochemistry and confocal microscopy. The effect of memantine (administered s.c. via osmotic minipump for 9 days) was determined in a separate group of Aß$_{1-40}$-treated rats.

Results: Seven days after the injection of Aß$_{1-40}$, an increase in the number of Bcl-2 immunoreactive cells at the injection site and occasionally in surrounding areas was detected. Aß$_{1-40}$ did not alter the expression of either Bax or Bad. Memantine decreased the number of TUNEL positive cells and the size of Aß$_{1-40}$ lesion in the hippocampus, and it also reduced the number of cells immunoreactive for Bcl-2.

Conclusion: These data indicate that memantine provides neuroprotection against Aß$_{1-40}$-induced toxicity by preventing the activation of the degenerative processes that trigger the expression of Bcl-2.

Source(s) of Funding: Forest Laboratories, Inc.

POSTER NO. 144

LET THE HAMILTON RATING SCALE FOR DEPRESSION SPEAK FOR ITSELF

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The Hamilton Depression Rating scale (HAM-D) has more than its share of critics. Are these criticisms well deserved? A review was conducted of the four seminal works related to the HAM- D, including the 1960 and the 1967 papers by Hamilton, the 1976 ECDEU Assessment Manual for Psychopharmacology, edited by William Guy, and the 1988 article by Janet B.W. Williams on the Structured Interview Guide for the HAM- D, the SIGH-D. When compared and contrasted, the articles reveal that the origin of the dissatisfaction with this scale may lie not with the HAM- D as it was originally validated, but instead with the current version of the HAM-D as it is familiar, accepted, and presently being used by all.

Hamilton gave specific rating guidelines in both his 1960 and his 1967 papers; these guidelines will be directly contrasted with the HAM- D as it is now used. Direct quotes from Hamilton's 1960 and 1967 articles, William Guy's ECDEU Manual, and Janet Williams' article on the SIGH-D demonstrate that what has been widely believed to be the authorized version of the HAM- D clearly is not.

Hamilton gave explicit directions for the HAM- D to be done by two raters. There is a multitude of evidence for this recommendation including excerpts from Janet Williams' article admitting that her structured interview administered by one clinician has lower reliability than the joint assessment intended by Hamilton. In addition, the scoring guidelines given by Hamilton are contrasted with the anchors that have been used since 1976. It is clear that the rating guidelines that were validated by Hamilton in his 1960 and 1967 article are not the anchors that were attributed to him by Guy, by Williams, and subsequently by the rest of us. Finally, the 1967 article specifically noted that "difficulty in concentration and forgetfulness" should be measured as part of item 10, Anxiety (psychic symptoms). However, because of the layout and the choice of anchors in the version that we use, diminished ability to concentrate, one of the nine recognized diagnostic criteria for a Major Depressive Episode, is not consistently measured.

This article demonstrates that the HAM-D has been altered. If the Hamilton Rating Scale for Depression used the guidelines specifically detailed by Max Hamilton in 1960 and then modified by him in 1967, it would be a more accurate and precise tool.

POSTER NO. 145

A 26-WEEK, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF DIVALPROEX SODIUM ER AUGMENTATION OF DONEPEZIL FOR COGNITION AND BEHAVIOR IN MILD/MODERATE ALZHEIMER'S DISEASE

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Objective/Background: Divalproex sodium has been studied in terms of decreasing the behavioral complications in AD patients; however, no clinical data exists on the cognitive enhancing ability of Divalproex sodium, despite some positive basic science data. This protocol provides data on the use of Divalproex sodium ER as an augmenting agent to donepezil for improving cognition (assessed with the ADAS-cog) in mild/moderate AD patients. Changes in behavioral complications (Neuropsychiatric Inventory) were also examined.

Methods: Subjects were enrolled if they had a diagnosis of AD and had a Mini-Mental Status Examination (MMSE) score within the range of 10 to 24 inclusive at baseline. No concomitant psychotropics were allowed. Subjects were randomized to an 18-week double-blind treatment period of augmentation with Divalproex sodium ER or placebo.

Results: At baseline, the mean ADAS-cog score was 24.27 and the mean NPI score was 16.75. At week 26, the cohort on the combination of Divalproex sodium ER and donepezil versus the cohort on placebo and donepezil had the following results: ADAS-cog of 27.33 versus 32.00 and NPI of 8 versus 12.33.

Conclusion: This analysis of a double-blind, placebo-controlled trial of the augmentation of donepezil with divalproex sodium ER revealed a greater decrease in the NPI, consistent with clinical practice. However, of note is the greater stability in the ADAS-cog, which would be in concert with the basic science data to date.

Source(s) of Funding: Abbott Laboratories, Inc.

POSTER NO. 146

NATIONAL PATTERNS IN THE CONTINUITY OF ANTIDEPRESSANT TREATMENT FOR DEPRESSION

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Background: Although discontinuation of antidepressant therapy significantly undermines the efficacy of antidepressant medications, little is known about the rate and pattern of antidepressant discontinuations.

Methods: An analysis is presented of antidepressant therapy continuity from a nationally representative sample of adults during their first lifetime course of antidepressant treatment for depression. Longitudinal data are examined from the1996-1999 Medical Expenditure Panel Surveys (MEPSs), a national probability survey of the US civilian non-institutionalized population. The characteristics of three patient groups, ages 18 to 64 years, are compared: patients who discontinue antidepressant therapy for depression during the acute (0-30 days), continuation, (31-60 days), and maintenance (>60 days) phases of treatment.

Results: An approximately equal proportion of patients (N=752) discontinued antidepressant therapy during the acute (31.2%), continuation (32.9%), and maintenance (35.9%) phases of treatment. The risk of antidepressant therapy discontinuation during the acute phase of treatment was significantly greater for Hispanic than non-Hispanic patients (44.7% vs 30.0%, X^2=5.47, df=1, p=.02); patients with low rather than middle or high incomes (37.4% vs 28.1%, X^2=5.92, df=1, p=.015); and patients with 12 or fewer years of education compared to those with more education (40.5% vs 28.0%, df=1, df=1, p=.01). There was also a non-significant trend toward acute phase discontinuation among patients treated with tricyclics or other older antidepressants as compared with newer antidepressants (42.3% vs 29.1%, X^2=3.65, df=1, p=.056). The likelihood of continuing antidepressant therapy into the maintenance phase of treatment was significantly greater for women than men (39.5% vs 27.6% X^2=8.3, df=1, p=.004), patients who received concomitant psychotherapy (49.4% vs 31.6%, X^2=10.5, df=1, p=.001), and for patients with fair or poor rather than excellent, very good, or good self-rated mental health prior to treatment (43.9% vs 32.1, X^2=7.9, df=1, p=.005).

Conclusions: Discontinuation from antidepressant therapy is widespread in the community treatment of depression, especially among socioeconomically disadvantaged patients. Psychotherapy, pharmacological properties of the antidepressant, and initial illness severity may influence the duration of antidepressant treatment.

Significance: Greater attention should be focused on reducing discontinuation of antidepressant therapy, especially in clinical settings that serve low income and minority populations. Concomitant psychotherapy and appropriate antidepressant selection may improve the continuity of antidepressant therapy for depression.

POSTER NO. 147

CLINICAL COURSE OF CATIE PATIENTS

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This is the first report on clinical course over the 36 weeks from CATIE, a multicenter effectiveness trial of atypical antipsychotics for agitation and psychosis of AD outpatients that has just completed enrollment. The essential criterion for randomization was the clinicians' equipoise-based judgment that antipsychotic medication was indicated. Patients were first randomized to one of three antipsychotics or placebo. If indicated clinically or for lack of efficacy doses could be adjusted or subjects switched by double-blind randomized assignment to a second atypical or to citalopram. And, if this was ineffective, then they could be randomly but openly assigned to the third antipsychotic or citalopram. At any time, if clinically indicated, patients could be treated openly by clinicians' choices of medications.

Of 389 included in this analysis, 56% were women, 60% were married, mean age was 78 y, mean MMSE was 15, and 53% had spousal caregivers. Approximately 80% had delusions, 50% hallucinations, and 85% agitation, with 75-80% each moderately to markedly severe and occurring frequently or very frequently, using NPI ratings. Completion of either phase 1, 2 or the open phase 3 was taken as evidence of effectiveness of treatment since it implies clinical stability. On this basis 14%, 21%, and 30% completed each of the phases such that overall 33% could be considered responders with increasing likelihood over time. Overall 41% were entered into open choice, indicating unsatisfactory responses. Approximately 12% of patients entered nursing homes and 6% died. The clinical courses over 36 weeks contrast with clinical trials where antipsychotic treatment is maintained for 10-12 weeks before efficacy is assessed. Variations in clinical practice among the treating physicians contribute to some of the variability.

POSTER NO. 148

PRE-RANDOMIZATION WORSENING OF INDIVIDUAL SYMPTOMS OF DEPRESSION: DOES INCREASED ANXIETY PRIOR TO TREATMENT PREDICT PLACEBO RESPONSE?

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Objective/Background: We have previously reported that patients whose symptoms worsen prior to their randomization into clinical trials of depression show higher response to placebo post-randomization than do those whose scores remained stable during this same period (Evans et al., in press 2004). We have hypothesized that these "baseline worseners" may experience elevated anxiety during the no-treatment phase of the study (resulting in their elevated HAMD scores at baseline). Under this hypothesis, the onset of study procedures (irrespective of treatment group) helps to ameliorate these symptoms, which produces the enhanced response to both placebo and medication. In order to investigate this hypothesis we examined placebo response in patients who worsened in an anxiety cluster subset of HAMD items.

Methods: Four randomized, double-blind, placebo-controlled trials (active medication = fluoxetine or paroxetine) were conducted in outpatients with Major Depressive Disorder using a novel design in which a depressive severity inclusion criterion (HAMD > 22) was utilized only at Screen. Changes in HAMD scores between Screen and Baseline were analyzed to determine the degree of worsening that occurred on each item, allowing rank-ordering of items according to those showing worsening by the most patients. An anxiety cluster of HAMD items was established in which both anxiety and magnitude of worsening across the population was taken into account. Post-randomization placebo and drug response was determined for each study and in the collapsed data set for patients showing worsening in at least two of the five anxiety cluster items.

Results: Patients who worsened between Screen and Baseline in at least two of the HAMD anxiety cluster items (Anxiety psychic, Anxiety somatic, Agitation, Somatic/GI, and Insomnia late) showed higher placebo response and poorer drug-placebo separation than those patients who did not worsen in these items.

Conclusion: The present findings support the hypothesis that patients who worsen in anxiety-relevant symptoms during the run-in procedure to clinical trials of depression may be more prone to placebo response than those who show no such worsening. Caveats to this hypothesis and future research directions are discussed.

Source(s) of Funding: Boehringer Ingelheim, Axon Clinical Research.

POSTER NO. 149

A SURVEY OF CLINICIANS REGARDING THE TREATMENT OF ALZHEIMER'S DISEASE IN 2003

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Objective/Background: To better understand clinicians' beliefs and practices regarding the treatment of Alzheimer's disease.

Methods: Information was collected from clinicians attending a Psychiatry Update conference organized by Duke University in August, 2003 regarding the background of the clinicians, various choices of treatment options for Alzheimer's disease, and the use of cholinesterase inhibitors in particular.

Results: There were 149 respondents out of a survey sample of 400 clinicians (response rate 37.3%). 70.3% respondents were psychiatrists, 10.3% were primary care physicians, 9.0% were registered nurses, and 3.4% were nurse practitioners. 67.4% respondents ranked cholinesterase inhibitors as the most effective treatment for mild-to-moderate Alzheimer's disease. However, control of lipids and blood pressure (13.6%), aerobic exercise (7.9%), vitamins (7.2%), and Ginkgo biloba (4.5%) were considered by others to be the most effective treatment. 17.1% respondents did not consider cholinesterase inhibitors to be either the most effective or second-most effective treatment. Of the cholinesterase inhibitors, 42.0% considered donepezil to be the most effective agent for mild-moderate disease, while 40.6% had no preference. For moderate-severe disease, 20.3% thought donepezil was the most effective agent, while 54.5% had no preference. When one cholinesterase inhibitor failed to work, 71.4% would switch to another cholinesterase inhibitor. 18.6% would stop cholinergic therapy altogether, 7.9% would raise the dose higher than recommended, and 2.1% would add a second cholinesterase inhibitor. For vascular dementia, 70.1% had no preference among the cholinesterase inhibitors, while the others preferred one or the other. Respondents significantly tended to favor the same medication for mild and for moderate-severe disease ($p < 0.001$). Those with little or no experience with treating dementia were more likely to think that donepezil or rivastigmine were more effective than the other cholinesterase inhibitors in moderate-to-severe Alzheimer's disease ($p = 0.04$).

Conclusion: Further education on this topic is needed for a significant proportion of clinicians. Nearly a third of respondents did not think cholinesterase inhibitors are the most effective treatment for Alzheimer's disease, and about half of these did not even consider them to be the second-most effective treatment. Even though there is minimal data on these issues, a substantial proportion (45.5 to 59.4%) believe that one cholinesterase inhibitor is superior to the others, and endorsed different strategies after an initial trial of a cholinesterase inhibitor fails. Clinical trials addressing these common clinical questions are urgently needed in order to provide clinicians with evidence-based guidance.

Source(s) of Funding: None

POSTER NO. 150

IM ZIPRASIDONE IN AGITATED PATIENTS WITH BIPOLAR DIAGNOSES

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Objective: To evaluate the efficacy of IM ziprasidone in agitated patients with bipolar disorder or schizoaffective disorder bipolar type.

Methods: This was a subgroup analysis of 2 similarly designed, randomized, double-blind, fixed-dose, 24-hour studies of IM ziprasidone in agitated patients with bipolar disorder or schizoaffective disorder bipolar type. Patients received 2-mg control dose (n=15) vs 10 mg (n=20) and 2-mg control dose (n=11) vs 20 mg (n=15) (80 mg maximum). Efficacy was assessed by BARS, CGI-S, and PANSS Agitation items scores.

Results: The greatest reductions in agitation (mean change in BARS) at 2 hours and 4 hours post-first-dose were seen with 20-mg IM ziprasidone. At 4 hours, the greatest improvement in CGI-S was seen in the 20-mg ziprasidone group. Responder rates (=2 points decrease in BARS at 1.5 hours post-first-dose) were 80% in the 20-mg group (P=0.01 vs 2 mg) and 58% in the 10-mg group, similar to results in the primary studies. No dystonia or excessive sedation was reported in either dosage group; 1 patient in the 10-mg group experienced akathisia.

Conclusion: Ziprasidone at 10 and 20 mg IM was rapidly effective and well tolerated in agitated psychotic patients with bipolar spectrum diagnoses, with the 20-mg IM dose producing the largest decrease in agitation. The 10-mg dosage level is not consistently effective.

Source of Funding: Supported by funding from Pfizer Inc.

POSTER NO. 151

RESPONSE TO MEMANTINE TREATMENT BASED ON MULTIPLE DEFINITIONS OF RESPONDERS

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Background: Memantine, a low-moderate affinity, uncompetitive NMDA receptor antagonist, is a novel Alzheimer's disease (AD) therapy approved in the U.S. in October 2003 for the treatment of moderate to severe AD. A double-blind, placebo-controlled U.S. trial (24 weeks) tested the efficacy of memantine (10 mg b.i.d.) on global, functional and cognitive domains in 404 moderate to severe AD patients already on stable treatment with the cholinesterase inhibitor donepezil (ChEI). Memantine/ChEI treatment was shown to be efficacious compared to placebo/ ChEI (Tariot et al., 2004).

Objective: To examine the relationship between response rate and the criteria for response using multiple definitions of response (e.g., cognition, activities of daily living, global ratings, and behavior alone or in combination).

Methods/Design: response was defined as improvement or no change (stabilization) over the course of evaluation on the efficacy measures: SIB (cognitive), ADCS-ADL[19] (functional), NPI (behavior), and CIBIC-Plus (global). The statistical analysis was based on the ITT population using the last observation carried forward approach. Each variable was tested alone as a responder, and in combination. In some cases, response was defined with conditional definitions. Risk differences (response on placebo subtracted from response on memantine) was the outcome of interest.

Results: Most responder analyses were significantly in favor of memantine/ChEI treatment which was expected given that all of the individual measures were significant. The risk difference in response on either the ADCS-ADL[19], SIB, CIBIC-Plus or NPI ranged from 10-14%. When these variables were combined to dual responses, the range varied from 5-16%, indicating that combinations of response can both amplify and attenuate the risk difference. For example, on the SIB alone, the memantine/ChEI response rate was 11% better than placebo ($p=0.03$). When positive response on the SIB was required in conjunction with the NPI, the memantine/ChEI response rate was 16% greater than placebo/ChEI ($p<0.001$). When SIB response was combined with stability or improvement on the CIBIC-Plus, the response to memantine/ChEI was 9% greater than placebo/ChEI ($p=0.067$). When response was defined as improvement on any of the scales, the risk difference was 9% ($p=0.016$).

Conclusion: Collectively, the responder rates demonstrate that memantine treatment is superior to placebo treatment, regardless of how response was defined, though the risk difference varies depending on the exact definition.

Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I; Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA. 2004;291:317-324.

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POSTER NO. 152

HIGH-DOSE ZIPRASIDONE: EFFICACY AND TOLERABILITY IN CLINICAL PRACTICE

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Introduction: Ziprasidone's clinical development program evaluated safety and tolerability at dosages =200 mg/d. Limited data on higher dosages are available. We review ongoing clinical experience at dosages =480 mg/d.

Methods: Variously diagnosed patients given ziprasidone 240 mg/d met the following criteria: (1) treatment-resistant history, (2) robust but incomplete response at ziprasidone 160 mg/d, and (3) minimal side effects. Similar criteria were applied to patients advanced stepwise to ziprasidone 320, 400, and 480 mg/d. An electronic medical record, Behavior 2003, allowed analysis of dosages, demographics, diagnoses, efficacy, and adverse events.

Results: A total of 51 patients received ziprasidone =240 mg/d for =18 months, 37 for =14 days and a minimum of 3 visits; ages ranged from 19-84 years, with 5 patients =60 years old. Of these, 21 (ages 19-62 years) were advanced to ziprasidone 320 mg/d, 3 (ages 20-36 years) then to 400 mg/d, and 2 (age 36-48 years) then to 480 mg/d. Most patients improved in primary illness severity (Likert scale, clinician rated). Improvements in negative, depressive, and anxiety symptoms were particularly noteworthy. Treatment was well tolerated; no patients discontinued due to AEs. No clinically significant ECG changes were observed.

Conclusion: Treatment-resistant patients who partially respond to ziprasidone at 160 mg/d may benefit from dosages as high as 480 mg/d, with good toleration.

Source of Funding: Supported by funding from Pfizer Inc

POSTER NO. 153

AN ITEM RESPONSE THEORY ANALYSIS OF THE HAMILTON DEPRESSION RATING SCALE: GENDER DIFFERENCES IN MEASURING DEPRESSION SEVERITY

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Objective/Background: Item Response Theory (IRT) analyses can be utilized to determine whether there is systematic bias in responding on clinical scales across two or more groups. Consequently, we examined whether there were any gender differences in ratings on items of the Hamilton Depression Ratings Scale (HDRS) in patients with Major Depressive Disorder (MDD).

Methods: Data from four randomized, double-blind, placebo-controlled studies of the treatment of MDD were combined for analyses. Two pharmaceutical companies provided data from each of two studies carried out in the United States between 1996 and 2000 with male and female outpatients (18-65 yrs; N=1233). The treatment periods were 6-8 weeks in length. Entry criteria required a diagnosis of MDD (DSM-IV) and minimum scores of 15 (one study) or 20 (three studies) on the 17-item HDRS. For IRT analyses, the TESTGRAF software developed by Ramsay was used to generate item characteristic curves (ICCs) and option characteristic curves (OCCs). The ICCs provide a graphical illustration of the expected score on a particular item as a function of overall severity. Each OCC relates the probability of receiving a particular rating on an item given the overall level of severity. The ICCs and OCCs generated from data provided by males were compared to those provided by females.

Results: There was no systematic difference between males and females on the great majority of items of the HDRS. On the genital symptoms (GS) item, however, females were rated higher than males across the entire range of severity. The OCCs revealed that males had a higher probability of receiving a rating of '0' than females, while females had a higher probability of receiving a rating of '2' than males across the range of depression severity; there was no difference in the probability of receiving a rating of '1'.

Conclusion: There was a systematic gender difference in responding on the GS item. A number of explanations could potentially account for this difference. The anchors of the GS item are such that it may be easier for raters to give points when the patient is female. Menstrual symptoms may be considered as GS by some raters (despite any instructions raters may have been given to the contrary). SSRIs commonly produce orgasm dysfunction, and females may be more likely to report this than males. Finally, males may generally be less likely to admit to GS than females.

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POSTER NO. 154

ASSESSMENT OF SEROTONIN TYPE 1A (5-HT1A) RECEPTOR GENOTYPE IN A NORMAL VERSUS A DEPRESSED POPULATION AND THE RELATIONSHIP TO PREDICTABILITY OF ANTIDEPRESSANT RESPONSIVENESS

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Objective/Background: This study was designed to determine the allelic frequency of six 5-HT1A receptor polymorphisms in a depressed versus a non-depressed population, and in SSRI antidepressant responders versus SSRI non-responders.

Methods: 132 subjects with major depression were recruited between January - December 2002. 100 subjects were considered SSRI responders, and 32 were considered SSRI non-responders who ultimately responded to a non-SSRI treatment regimen. Subjects were mostly of Caucasian or African American descent. 100 non-depressed controls were obtained from DNA samples used in other ongoing genetic studies. DNA was obtained from buccal cells and isolated. Genotyping was performed using pyrosequencing. Individual association studies were performed on six previously reported structural polymorphisms. Statistical analysis was performed using SAS.

Results: Four of the six single nucleotide polymorphisms were identified in the study groups. No variants were found in the Pro16Leu or Gly22Ser polymorphisms. Results of Ile28Val and Pro184Leu both produced similar allelic frequencies as previously reported (0.43% and 5.4%, respectively). The frequency for the rare Arg220Leu polymorphism was 2.64%. The Gly273Asp polymorphism resulted in a frequency of 0.43% (previous studies reported frequencies ranging from 0% in a Spanish population to 5-8% in Japanese). No homozygote variants were observed in any group. No statistical differences in variant allelic frequencies were found between the SSRI responders, SSRI non-responders, and the non-depressed control group.

Conclusion: The six currently identified non-synonymous polymorphisms in the 5HT1A receptor did not result in differing polymorphic frequencies in a depressed versus non-depressed population, nor between SSRI responders versus SSRI non-responders.

Source(s) of Funding: ACCP 2001 Wyeth-Ayerst Psychopharmacy Fellowship Grant Partial funding/support also received from NIH AG 10485.

POSTER NO. 155

NEW SADHART ANALYSIS: POST MI DEPRESSION, A CAUSE OR CONSEQUENCE OF MYOCARDIAL INFARCTION

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Background: Although depression co-exists with a number of medical and psychiatric conditions, heart disease is unique. Depression increases the risk of cardiac death. Following hospitalization for MI, depression increases the risk of dying by 350%. Also striking is that 20% of post MI patients show evidence of major depressive disorder (MDD). Epidemiological studies show that prior episodes of MDD predicts chronicity in the year after MI, while first episode cases are likely to remit and not relapse. This analysis examines these coronary associated depressions and their response to drug in an attempt to expand our understanding of the link between depression and acute coronary syndromes. Additionally, decreased heart rate variability (HRV) is associated with increased post MI mortality and is significantly diminished in MDD. The association between time of onset of MDD and HRV, as well as changes in HRV with treatment were examined.

Methods: SADHART examined the safety and efficacy of sertraline after MI as a step to test if antidepressant treatment would reduce mortality. Subject data from SADHART were analyzed to examine the differences in the time of onset of depression and response to treatment with sertraline, as well as effect of setraline vs. placebo on HRV.

Conclusion: Results of SADHART found no evidence of harm with sertraline, a drug benefit, and a suggestive 23% reduction in life-threatening events. Of 3356 hospitalized acute coronary syndrome patients, interview revealed 556 (17%) met modified criteria for MDD and of these, a disproportionate, 36% were female. Prior studies observed MDD in the hospital and followed cases prospectively; however, SADHART indicates 53% of cases began before hospitalization. Cases starting in the hospital showed a higher placebo response (60% vs 46%, $p<.01$), were more likely male and had little drug effect (69 vs 60%). Depressions beginning before hospitalization showed a significant drug effect (63% vs 46%). When combined with the previously observed influence of prior episodes of depression, there was a robust sertraline/placebo difference (73% vs 43%; OR = 3.5 (1.56-7.92)). These data suggest a dichotomy among coronary depressions. The more than 50% of cases beginning before hospitalization and/or with a prior history, rather than resulting from the stress of MI, could conceivably be contributing to the onset of the infarct. They are more likely female, have a poor placebo response, but show a robust response to sertraline. Although there is a strong suggestion that SSRI treatment reduces mortality, at present it is unclear if the mortality risk is influenced by this dichotomy. Among the sample, all of who had MDD, those cases developing before hospitalization and with prior episodes have the lowest HRV. This variability improved with sertraline treatment.

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POSTER NO. 156

REDUCED MUSCARINIC CHOLINERGIC2 RECEPTOR BINDING IN BIPOLAR DISORDER USING PET AND [F-18]FP-TZTP.

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Introduction: The muscarinic-cholinergic system has been implicated in mood disorders by findings that, 1)cholinergic agonist administration results in exacerbation of depressive signs and symptoms, 2)muscarinic-cholinergic agonists, ACh releasing agents or acetylcholinesterase inhibitors induce exaggerated effects on REM density and latency in depressed subjects relative to healthy-controls and, 3)both manic and depressed bipolar (BD) subjects show increased pupillary sensitivity to the muscarinic-cholinergic agonist pilocarpine relative to controls. In addition, a recent study reports an association of a M_2 receptor polymorphism in females with Major Depressive Disorder (MDD). The current study investigated muscarinic-cholinergic receptor binding in mood disorders using PET and the novel radioligand, [18F]FP-TZTP, a muscarinic agonist that has been shown to be relatively selective for M_2-receptors. We hypothesized that the M_2-receptor, which functions predominantly as a presynaptic autoreceptor, would have decreased binding in mood disorders.

Methods: Central M_2-receptor DV was measured in the depressed state in vivo in 21 currently-depressed subjects (8 Bipolar Disorder, 14 Major Depressive Disorder) and 13 age matched healthy-controls (Mean SD: Age, HC 34 6.3; BD 32 5; MDD 36 7.5 years). ROI analysis of M_2-receptor images using [^{18}F]FP-TZTP and high resolution MRI was performed. Kinetic analysis used a one-tissue compartment model. Regional DV values were corrected for the plasma free fraction (f_1), and compared across groups using ANOVA.

Results: The mean DV of [^{18}F]FP-TZTP binding in BD subjects was 13-20% lower in all brain regions examined compared to healthy-controls, although, this did not reach statistical significance. A 20.7% reduction in [^{18}F]FP-TZTP DV of BD subjects compared to healthy controls did trend toward being significantly reduced ($t=1.722$; $p=0.101$). [18F]FP-TZTP DV was reduced by 18.7% in whole brain, 18.8% in orbital cortex, 17.3% in anterior cingulate cortex, 13.7% in ventral striatum, 15.3% in hippocampus, 14% in amygdala, and by 13% in cerebellum in BD subjects relative to controls. In contrast, in subjects with MDD, [^{18}F]FP-TZTP DV was non-significantly increased in all brain regions (4 to 7%) compared to that of controls. MANOVA generated a trend toward a significant effect in primary visual cortex, orbital cortex and ventral striatum.

Conclusion: [^{18}F]FP-TZTP binding may be decreased in BD relative to both the MDD and healthy-control groups. Additional subjects will be scanned to ascertain whether the observed reduction in [18F]FP-TZTP binding in BD subjects becomes statistically significant in a larger sample. Because [^{18}F]FP-TZTP is a receptor agonist, a reduction in [^{18}F]FP-TZTP DV/f_1 in BD subjects may reflect increased synaptic concentrations of acetylcholine. Alternatively, a lower DV could represent decreased M_2-receptor density and/or increased affinity (K_d). Because M_2-receptors are predominantly presynaptic-autoreceptors which regulate release of ACh, a decrease in these or their availability could conceivably lead to a lack of regulatory control over presynaptic ACh release. A lack of regulatory control over release does agree with exaggerated responses to cholinomimetic agents, as evidenced during the depressed state of bipolar disorder.

POSTER NO. 157

SEVOFLURANE BURST SUPPRESSION THERAPY FOR TREATMENT-RESISTANT DEPRESSION

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Introduction: Burst suppression (electrocerebral silence) can be induced by inhalational anesthetic agents and limited results have suggested that this treatment is as effective as electroconvulsive therapy for treatment-resistant depression. Burst suppression therapy (BST) has the advantage that it produces no apparent cognitive side effects.

Methods: Forty patients with treatment resistant major depression were treated with sevoflurane BST while maintaining their stable medication regimens. 17 subjects had unipolar major depression, 22 subjects had bipolar depression, and one had schizoaffective depression. 9 of these subjects had psychotic depression. All subjects had failed adequate trials of at least three antidepressant medications. 25 subjects had previously been treated with ECT, and 9 of these patients were ECT non-responders.

Results: In this very treatment-resistant sample, 78% had a 50% reduction in HRSD-17 item (response) and 65% had a HRSD-17 of < 10 (remission). This is in the range of responses reported for ECT in treatment-resistant patients. 78% of patients with psychotic depression responded, as did 55% of ECT non-responders. Response rates were also similar on the Beck Depression Inventory and generally occurred by four treatments. Subjective memory, as rated by the Squire Subjective Memory Scale, improved with treatment. Side effects were minimal and virtually all patients preferred this treatment to ECT. All but one of the patients who were previously treated with ECT thought that BST was more effective.

Discussion: BST appears to be a safe and effective treatment for treatment-resistant depression. The response rate is comparable to ECT, it is well tolerated, and does not appear to have any subjective cognitive side effects. BST is a promising therapeutic alternative to ECT.

POSTER NO. 158

ARE THERE DIFFERENCES BETWEEN DEPRESSED PSYCHIATRIC OUTPATIENTS WHO WOULD AND WOULD NOT QUALIFY FOR AN ANTIDEPRESSANT EFFICACY TRIAL?

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Objective/Background: The impact of efficacy study inclusion and exclusion criteria on the representativeness of samples included has begun to receive study. Two studies examined how many patients applying for an acute phase efficacy trial are accepted into the trial, and found low acceptance rates (Partonen et al., 1996; Keitner et al, 2003). Previously, our group examined the representativeness of antidepressant efficacy trials (AETs) by applying typically used exclusion criteria to a large sample of depressed outpatients, and found that most depressed patients treated in routine clinical practice would not have qualified for an AET (Zimmerman et al., 2002). In the present report we turn to the question of the comparability of the clinical characteristics and psychosocial functioning of patients who would and would not qualify for an AET.

Methods: 599 patients with a principal diagnosis of DSM-IV nonbipolar, nonpsychotic major depressive disorder (MDD) were interviewed by a trained diagnostic rater who administered the SCID and the Hamilton Depression Scale. The interview also included items from the SADS on social and occupational functioning. We determined the number of episodes, duration of the current episode, age of onset, and lifetime history of suicide attempts and hospitalizations. Nearly two-thirds (382) of the patients were interviewed with the SIDP for personality disorders.

Results: We compared demographic, psychosocial and clinical characteristics of the 123 patients who would qualify for an AET, 289 whose symptom severity was too mild to qualify for an AET, and the 187 patients who would be excluded because they were suicidal or had a comorbid anxiety or substance use disorder. There were few differences between the included patients and the low severity-excluded group. In contrast, compared to the included patients the patients who would be excluded due to comorbidity or suicidal ideation had more social impairment, more frequently missed work because of psychiatric reasons, experienced more prior episodes, were more likely to have an episode duration of greater than two years, made more suicide attempts, and were more likely to have a cluster B and cluster C personality disorder.

Conclusion: Recent studies have demonstrated that a large percentage of patients who apply for AETs are excluded from participation. In addition, the majority of patients treated in clinical practice would not qualify for most AETs. The present report extends the findings of these studies by demonstrating that the clinical and psychosocial profile of patients who would be excluded from an AET because of comorbid anxiety or substance use disorder or significant suicidal ideation differs from that of patients who would qualify for a trial. Specifically, we found that these excluded patients are a more chronically ill group with more prior episodes, greater social and occupational impairment, and more personality pathology. The findings of the present study raise additional caution in generalizing the results from AETs to clinical populations.

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POSTER NO. 159

RECURRING SYMPTOMS ACROSS CONSECUTIVE EPISODES OF MAJOR DEPRESSION

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Introduction: Unipolar major depressive disorder (MDD) is characterized by relapses and recurrences in a majority of individuals, with no established predictors of course other than the previous course itself. Aim of the present study was to investigate the stability of depressive symptoms across recurrent episodes of MDD. Identifying recurrent symptoms could be clinically helpful in early identification and treatment of recurrences and could point to treatment-relevant depression subtypes that are stable over time in the same patients.

Methods: 233 women with recurrent unipolar disorder were enrolled for the treatment of an acute depressive episode, until stable remission, with interpersonal psychotherapy (IPT) and, for a subsample, with a combination of IPT and pharmacotherapy (fluoxetine). 135 patients achieved a stable remission and entered a 2 year maintenance phase in which they were treated with maintenance IPT (IPT-M). 34 subjects presented a recurrence of MDD during the maintenance period. We examined the agreement between symptoms at the outset of acute treatment (baseline) when the subjects had been ill for an average of 26.8±20.1 weeks, and at the time of recurrence, when subjects had been ill for less than 4 weeks. Total and individual item scores on the Hamilton Rating Scale for Depression (HRS-D) recorded on the day when the recurrence was established were compared to baseline HRS-D total and item scores, using quadratic-weighted kappa coefficients.

Results: No significant differences in demographic or clinical characteristics were found between the 34 patients with a recurrence and the rest of the group. HRS-D total scores did not differ significantly between the index and recurrent episode. Significant kappa coefficients across the two consecutive episodes were reported for the following items: guilt feelngs ($_k$=0.43); oversleeping ($_k$=0.45); anergia ($_k$=0.34); and loss of libido ($_k$=0.28).

Conclusion: The recurrent course that frequently characterizes MDD has been recently associated with higher severity, risk of impairment and treatment resistance. Few studies have focused on the detection of recurrent symptoms across depressive episodes in the same subjects followed longitudinally. The few available studies mainly focused on validating depressive subtypes. We found that in women, at least, guilt, oversleeping, anergia, and loss of libido, are consistent across consecutive episodes and are apparent early in the course of the new episode, suggesting that these may be important warning signals of impending recurrence.

POSTER NO. 160

INCREASED RESPONSE TO PHARMACOTHERAPY IN CHILDHOOD MDD WITH FLEXIBLE DOSE AND EXTENDED TREATMENT: A PRELIMINARY REPORT

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Objective/Background: Children and adolescents were treated open label with fluoxetine for up to 12 weeks. Response rates and serum total fluoxetine are reported. Objectives: To determine overall response rate and associated fluoxetine levels for 12 weeks of open label treatment allowing for flexible dosing.

Methods: 100 children with MDD were enrolled in a NIMH funded study of remission and relapse (PI: Emslie). Each child completed a two-week (three visit) diagnostic evaluation to verify eligibility for enrollment including the K-SADS-PL. The research group reviewed each case to reach a consensus on overall diagnosis and individual symptoms. Enrollment required DSM-IV diagnosis of MDD based on the K-SADS-PL and a CDRS-R >= 40 and CGI >= 4. The primary outcome measures for this study were the CDRS-R and the CGI-I at week 12 or early termination. Subjects began on 10mg for one week and then increased to 20 mg. At Week 6 the clinician could increase to 40 mg based on inadequate clinical response.

Results: 17 subjects did not make it to Week 12 (4 adverse events, 3 lack of efficacy, 7 withdrawn by parent/patient, 1 non-compliance, 1 moved, 1 lost to follow-up). Based on LOCF, 42% had a final dose of either 30 or 40mg. The response rate at Week 6 was 74.8% (based on CGI-I <= 2) and 81.8% by week 12. Of those terminated early, 71% had their dose raised to 30 or 40 mg. A subset of n=70 had both Week 6 and Week 12 total fluoxetine serum levels (Week 6 Low Dose [10-20mg] = 251 ± 102; High dose [30-40mg] = 200 ± 81, p = ns). Week 12 total fluoxetine Low Dose = 240 ± 125 and High Dose = 334 ± 150ng/ml, $F(1,64) = 4.4$, $p = .04$.

Conclusion: Maintaining fluoxetine treatment for up to 12 weeks and increasing the dose at approximately 6 weeks after minimal response improved the overall response rate to 81.8%. Data supports the importance of allowing for adequate time for response to occur (up to 6-10 weeks) and that increasing the dose at that time for non or partial responders results in improvement of response for an additional number of individuals.

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POSTER NO. 161

A REVIEW OF SSRI COMPARISON TRIALS

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Objective/Background: As a class, the selective serotonic reuptake inhibitors (SSRIs) are the most frequently prescribed antidepressant medications. Reviews of studies that have directly compared the SSRIs have failed to find evidence of differences in efficacy. There are now 28 published comparisons of SSRIs. We review this literature and determine response rates across studies in order to estimate response rates to guide researchers in determining appropriate sample sizes for drug-drug comparison studies.

Methods: In summarizing the results of these studies we focused on outcome at endpoint based on intent to treat analyses. Almost all studies used multiple outcome measures. In fact, the data from a single measure was often analyzed in several ways. For example, studies using the Hamilton Rating Scale for Depression (HRSD), the most frequently used symptom severity outcome scale, have examined change in total scores, change in HRSD factor scores, change in the scores on each of the individual items, percentage of patients whose total score improved by at least 50%, and percentage of patients who scored below a cutoff score at the end of treatment. The number of outcome comparisons in the 28 studies ranged from 1 to 41, with a total of 394 outcome variables examined (mean=14.1).

Results: In 6 (21.4%) studies one SSRI was significantly more effective than another on at least one outcome measure. Across studies, there were significant differences between SSRIs on 11 of the 394 (2.8%) outcome variables, less than what would be expected based on chance alone. We computed the response rates for each medication across studies and found that for each SSRI (except fluvoxamine for which data was available from only a single small study) the responder rate was between 60% and 70% (citalopram-69%; fluoxetine-63%; paroxetine-63%; sertraline-67%). To detect a difference in response rates of 63% vs. 69%, the maximum difference between the medications, with a power of .80 and a two-sided alpha level of .05, approximately 1,000 subjects would be needed in each group.

Conclusion: Studies comparing the SSRIs have been underpowered to find differences between medications. Power analyses should be included and discussed in studies comparing medications.

Source(s) of Funding: none

POSTER NO. 162

STEADY-STATE BIOEQUIVALENCE OF ONCE-DAILY AND TWICE DAILY TABLET FORMULATIONS OF BUPROPION HCL

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Introduction: Wellbutrin® XL, in 150mg and 300mg strengths, has been developed and approved for once-daily administration in the treatment of major depressive disorder. This study was conducted to investigate bioequivalence of the new product to the twice-daily product (SR) under steady-state, fasting conditions.

Methods: A 300 mg dose of the new product given once daily to 49 healthy volunteers for 14 days was compared to SR given 150 mg b.i.d in a randomized crossover design. Each treatment included a 3-day titration phase and the two study periods were separated by a 14-day washout. Blood was collected over 24 hours and plasma was assayed by LC/MS/MS for bupropion, hydroxybupropion, threohydrobupropion and erythrohydrobupropion. Pharmacological Activity Weighted Composite (PAWC) was also calculated by adding concentrations of the 4 analytes corrected for molecular weight and relative pharmacological activity (mouse anti-tetrabenazine model). Non-compartmental methods were used to derive pharmacokinetic parameters, which were subjected to ANOVA; 90% geometric confidence intervals were constructed for AUC0(0-tau) and C_{max} of all analytes and PAWC to assess bioequivalence.

Results: Bioavailability of the XL formulation relative to SR was 90% based on AUC0(0-tau) for bupropion, each of its metabolites and PAWC. The AUC0(0-tau) relative ratio for all metabolites and PAWC was approximately 90%. The 90% geometric confidence intervals of AUC0- , C_{max} and C_{min} for all analytes and PAWC were within 80-125%. Bupropion primary pharmacokinetic parameters (mean ± SD):

Pharmacokinetic Parameters	Wellbutrin® XL Tablets, 300 mg qd	Zyban® Tablets, 150 mg bid
AUC0(0-tau) (ng*hr/mL)	1464.21 ± 411.73	1617.72 ± 435.84
C_{max} (ng/mL)	148.81 ± 38.84	141.65 ± 40.18
C_{min} (ng/mL)	24.50 ± 8.69	26.85 ± 9.47

Conclusions: The new once-daily formulation of bupropion HCl was found to be bioequivalent to the twice-daily product under steady-state, fasting conditions. Availability of the once daily product may improve patient compliance over the twice-daily formulation.

Source of Funding: Biovail Corporation funded this study.

POSTER NO. 163

ABSENCE OF SEXUAL DYSFUNCTION IN PATIENTS WITH MDD TREATED WITH GEPIRONE-ER

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Objective/Background: To determine the effect of gepirone-ER, a 5-HT1A agonist with demonstrated efficacy for the treatment of MDD on sexual function (SF), based on sexual outcomes assessments from 4 completed placebo-controlled studies.

Methods: Of 4 completed studies, 3 (placebo-controlled) assessed sexual functioning using the Derogatis Inventory of Sexual Function - Self-Report (DISF-SR), and 1 (fluoxetine and placebo-controlled) utilized the DISF interview with formal diagnosis of DSM-IV sexual disorders.

Results: In all 4 studies, the DISF score improved during acute or long-term treatment with gepirone-ER, as compared to placebo. When sexual disorders were formally diagnosed, the percentage of subjects who had no sexual disorders at baseline, but who developed a treatment emergent sexual disorder, was 6.33% for subjects who received gepirone-ER, 7.69% for subjects who received placebo, and 25.74% for subjects who received fluoxetine. Conclusion: In contrast to fluoxetine, gepirone-ER treatment is not associated with treatment-emergent sexual disorders. Furthermore, the quality of life as it relates to sexual function does not appear to be adversely affected by gepirone-ER treatment.

Source(s) of Funding: Organon Pharmaceuticals

POSTER NO. 164

AGE EFFECT ON CITALOPRAM DISPOSITION DEFINED BY A POPULATION PHARMACOKINETIC ANALYSIS

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Background: To develop a population pharmacokinetic model for citalopram, evaluating covariate effects on disposition in clinic patients aged 22 to 93.

Methods: A total of 106 patients from two study groups comprising ages ranging from 22 to 93 years (MEAN SD: 65.90 19.39) and weights ranging from 42.9 to 126.25kg (MEAN SD: 79.94 18.08), received citalopram 5mg to 60mg PO daily. A total of 199 plasma samples were available, with 114 samples from patients with age 74 to 93 years and 85 samples from patients with aged 22 to 65 years. The number of samples/subject ranged from 1 to 3. A mixed effects population pharmacokinetic model was constructed from these data using NONMEM . One and two compartment open pharmacokinetic models with various models for inter-individual variability and intra-individual variability were tested during model development. Generalized additive modeling (GAM) technique was applied for covariate model development. Xpose was applied for evaluating the goodness of fit plots and visualizing the model development.

Results: A one-compartment linear model with additive and proportional error adequately described the data. Both weight and age had a significant impact on clearance (CL) and volume of distribution (Vd). As age increased, CL decreased, half-life (t1/2) increased and AUC increased. The population predicted mean for CL, t1/2 and AUC/dose was 16.4 L/h, 155.8h, 69.67 mg h/L for younger group and 6.1L/h, 284.7h, 189.6 mg h/L for elderly group. The population prediction mean CL decreased across whole age range from 20.5L/h at 22 years of age to 2.02L/h at 93 years of age.

Conclusions: Age is a significant covariate on citalopram CL and Vd. The age effect persists across the entire age range. Special attention should be paid for elderly patients when dosing citalopram, as there may be at higher risk for an increased exposure to the drug according to the longer t1/2 and higher AUC for any given dose.

Source of funding: Supported by NIMH (P30 MH30915), NIBIB (9 P41 EB001975-06), MH65416, MH64173, MH52247 and Forest Pharmaceuticals.

POSTER NO. 165

ESCITALOPRAM IN THE LONG-TERM TREATMENT OF GENERALIZED ANXIETY DISORDER

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Objective/Background: Patients completing any of the 8-week trials were given the option of entering an open-label, flexible-dose trial to evaluate the long-term efficacy and tolerability of escitalopram in the treatment of GAD.

Methods: This was a 24-week, open-label, flexible-dose trial of escitalopram 10-20 mg/day. Efficacy assessments included HAMA, Clinical Global Impressions (CGI), and Quality of Life (QOL) scales. Response was defined as a CGI-Improvement score of 1 or 2.

Results: A total of 526 patients entered this open-label study. Of these, 299 (57%) completed 24 weeks of treatment. The mean HAMA score at baseline was 13.1. Long-term escitalopram treatment led to continuing improvement in all anxiety and QOL scores. Mean HAMA scores at week 24 for all study completers was 6.9, and 92% of completers were responders. Insufficient therapeutic response led to withdrawal of 4.2% of patients. No tolerability concerns were associated with long-term escitalopram treatment. Treatment-emergent adverse events in the present study were similar in type and frequency to those observed in the acute GAD trials. Adverse events led to withdrawal of 9.9% of patients.

Conclusion: These results support the long-term tolerability and effectiveness of escitalopram in the treatment of GAD.

Source(s) of Funding: Forest Labs

POSTER NO. 166

HEPATIC MONITORING IN CLINICAL TRIALS: A CASE STUDY

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Background: Development of new drugs requires sensitive and specific monitoring of patient biomarkers during clinical trials for potential drug-related hepatic effects. Currently analytes used in monitoring include alanine aminotransferase (ALT/SGPT), aspartate transaminase (AST/SGOT), gamma glutamyltransferase (GGT), total bilirubin (TBILI), and alkaline phosphatase (ALKPH).

Methods: The criteria for potential serious liver injury used in monitoring clinical trials was the presence of an ALT = 3X upper limit of normal [ULN] with a TBILI = 1.5X ULN. Lesser safety signals included sole elevations of ALT = 3X ULN, AST = 5X ULN or TBILI = 1.5X ULN. Comprehensive surveillance of patients meeting these criteria during the trial included a collection of patient characteristics, adverse events, concomitant medications, and other pre-existing conditions. Hepatic analytes for these patients were monitored closely until values returned to baseline. Mean and categorical changes of ALT, AST, GGT, TBILI, and ALKPH were compared for those on study drug versus placebo. The change in these analyte values from baseline to endpoint and maximum were calculated and displayed in "shift tables" to show categorical changes. Patients who had an ALT =3X ULN or had a TBILI = 1.5X ULN were identified.

Results: 88.4% and 88.7% of patients on study drug and placebo respectively, had normal ALT values at baseline. Of those, 1.05% and 0.2% on study drug and placebo respectively had a maximum post baseline ALT > 3X ULN and the difference in change from baseline to maximum elevation between study drug and placebo groups was statistically significant. 99.8% and 99.7% of patients on study drug and placebo respectively had normal TBILI values at baseline. Of those, 0.2% and 0.1% on study drug and placebo respectively had a maximum post baseline TBILI > 1.5X ULN and the difference in change from baseline to maximum elevation between study drug and placebo groups was not statistically significant.

Summary: Rigorous analyses and monitoring of patients allowed discrimination between possible study drug effects and the background variability of elevation in analytes traditionally used to identify liver injury. Comprehensive follow-up of these cases revealed other factors that may have contributed to these elevations. Pre-approval studies are not powered to detect serious drug-related hepatotoxicity. Therefore, it is critical to plan an analysis of analyte data to identify lesser potential hepatotoxicity signals and to follow-up those patients who have abnormal analyte findings during the study.

Source of funding: Eli Lilly and Company

POSTER NO. 167

CHROMIUM PICOLINATE: ATYPICAL DEPRESSION, CARBOHYDRATE CRAVING AND CLINICAL RESPONSE

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Depression is closely linked to disorders of glucose regulation. In a small pilot study chromium picolinate (CrPic), thought to enhance insulin sensitivity, reduced depression in atypical depressives significantly greater than placebo. Case studies of patients with diverse presentations, unresponsive to standard medications, and having carbohydrate craving as a common factor, report excellent response to CrPic.

Based on these findings, a Phase II type study was conducted on the efficacy of CrPic in atypical depression and the relationship of carbohydrate craving to clinical response.

Patients (n=113) with atypical depression were assigned by 2 to 1 randomization to CrPic or placebo in an 8-week double blind study. Both ITT (n = 110) and evaluable patient (EP) analyses (n = 75) were conducted. ITT was defined as all patients enrolled; EP received > 80% of the assigned drug.

Assessments included the 29-item Hamilton Depression Scale, Atypical Depression Diagnostic Scale, adverse events, vital signs and basic laboratory data.

Results:

1. There were no differences between CrPic and placebo for either ITT or EP analysis for change in total HAM-D or responder analysis (HAM-D reduction >50%; CGI = 1 or 2). Both groups showed positive response. The CrPic group, however, had significantly greater improvement in carbohydrate craving; weight change perception and rejection sensitivity. There were no differences favoring placebo. Based on the presumed mechanism of action of CrPic, when patients with blood glucose levels above 140 mg/dL (n=5) were excluded from EP analyses, the CrPic group had a significantly greater responder rate than the PBO group (55% vs. 28.5%, p<.04)

2. Carbohydrate craving at baseline had a highly significant relationship to clinical response. CrPic and placebo groups were equivalent for baseline carbohydrate craving levels. However, carbohydrate craving effect differed in the two groups.
   I. Level of carbohydrate craving significantly related to HAM-D reduction in CrPic but not PBO treated patients (P<.0006) with a positive correlation in CrPic patients of carbohydrate craving and clinical response (p<.0003).
   II. CrPic patients with severe carbohydrate craving had a significantly greater responder rate than PBO treated patients. (ITT: 65% vs. 33%, p<.05; EP 80% vs. 37.5%, p<.05)

3. There were no differences between PBO and CrPic groups for any AE's including weight gain or sexual dysfunction.

Discussion:

CrPic may be an effective, safe and highly tolerable antidepressant in patients with elevated carbohydrate craving.

Disclosure/Source of Funding: Nutrition 21, Inc.

POSTER NO. 168

CORRELATES OF CLINICIAN RATED AND SELF REPORT MEASURES OF DEPRESSION SYMPTOMATOLOGY IN PATIENTS RECEIVING ECT

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Introduction: The primary aim of this study was to determine the degree of correlation between the clinician-rated Hamilton Rating Scale for Depression-24 item (HRSD24) and the Inventory of Depressive Symptomatology-Self Report (IDS-SR30), a patient self report instrument.

Methods: As of 2003, 444 patients had received an acute course of ECT as part of the ongoing NIH-supported, multicenter trial of the efficacy and safety of continuation ECT vs pharmacotherapy (nortriptypline+lithium) in the prevention of relapse in patients with major depressive disorder. These patients had an average age of 55.6 years, 68.2% were female, and 29.7% were psychotic. HRSD24 measurements for all 444 subjects were obtained at baseline and after each ECT (3x/week). Complete data for the IDS-SR30 for baseline and end of study was available for 139 participants. The correlation between the clinician-rated HRSD24 and the patient self-report IDS30 was measured using Pearson's and Spearman's correlation coefficients. The correlations were evaluated by gender and by age groups. Using the HRSD24 as the gold standard measure, the sensitivity of the IDS-SR30 in identifying improvement in depressive symptoms was determined.

Results: For the 139 participants having both IDS-SR30 and HRSD24 measurements at both time points, there was strong and statistically significant correlations for baseline, end, and change from baseline measurements (Pearson's correlations: baseline $r=0.57$; end $r=0.73$; change $r=0.68$, all p's <0.0001). The association between clinician evaluation and patient report for change scores ranged from 0.73 ($p<0.0001$) in the youngest group (18-45 years) to 0.54 ($p=0.007$) in the oldest group (65-85 years). For the 139 patients, only 2.2% (3/139) who showed improvement on HRSD failed to show improvement on IDS-SR30.

Conclusions: The significant correlations between the HRSD24 and the IDS-SR30 suggest that the IDS-SR30 is a valid and reliable measure of depression severity in depressed individuals receiving ECT.

Source of Funding: National Institute of Mental Health grant MH-55489, 55495, 55486, 55484

POSTER NO. 169

ESCITALOPRAM TREATMENT OF SSRI NON-RESPONDERS CAN LEAD TO REMISSION IN PATIENTS WHO FAIL INITIAL SSRI THERAPY

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Objective/Background: It may be desirable to switch patients failing one SSRI to another SSRI. Escitalopram has been shown to be effective in patients who failed to respond to citalopram.

Methods: Depressed outpatients (18-65 years; MADRS >= 22) were randomized to receive 8 weeks lead-in treat ment with open-label citalopram (20-60 mg/day; N=129), sertraline (50-200 mg/day; N=125), paroxetine (20-50 mg/day; N=125), or fluoxetine (20-80 mg/day; N=128). Non-responders (MADRS >12) were eligible for 8 weeks open-label escitalopram (10-20 mg/day) in a follow-on trial. Remission was defined as MADRS <= 10. LOCF results are presented.

Results: In the lead-in trial, the proportion of patients with MADRS <= 12 (responders) was similar for citalopram and sertraline (56% vs. 55%) and somewhat lower for paroxetine and fluoxetine (50% and 43%, respectively). Similar results were observed for proportion of patients with >= 50% reduction in MADRS scores: (citalopram 61%, sertraline 61%, paroxetine 51%, fluoxetine 50%). A total of 137 (of 248) SSRI non-responders switched to escitalopram, of whom 80% completed treatment. Following switch to escitalopram, remission rates were highest for patients switched from sertraline (65%), followed by patients switched from fluoxetine (44%), citalopram (42%), and paroxetine (42%). Escitalopram was well tolerated, with 6.6% discontinuation due to adverse events.

Conclusion: These data confirm that escitalopram can be effective in patients failing therapy with citalopram and other SSRIs. Patients who fail treatment with sertraline showed numerically better remission rates than patients failing treatment with other SSRIs.

Source(s) of Funding: Forest Labs

POSTER NO. 170

FRONTAL EEG PREDICTS CLINICAL RESPONSE TO SSRI TREATMENT IN MDD

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Objective/Background: Previous reports suggested that frontal EEG activity in the theta frequency band (4-8Hz) predicts antidepressant treatment response in subjects with major depressive disorder (MDD). However, these prior studies used EEGs collected from elaborate, full-head recordings using skilled EEG technicians to apply electrodes and to identify artifact-free periods of EEG for analysis. In contrast, for this work we used simple 4-channel EEGs collected by non-EEG personnel; using automated methods to eliminate artifacts. We investigated whether frontal theta activity predicts treatment response in MDD during flexible dose antidepressant treatment.

Methods: 36 outpatients meeting DSM-IV criteria for MDD (17 female (47.2%), mean age 37.5 +/- 11.5 years) entered an 8-week prospective treatment study with open-label, flexible dose SSRI antidepressants. The 17-item Hamilton Depression Rating Scale (HAM-D) was administered at baseline and at weeks 1, 4, and 8 during treatment to assess changes in depressive symptoms. We defined treatment response as Ham-D reduction >/= 50% from baseline to week 8. At each study visit (baseline, week 1, 4, and 8) we recorded serial, 4-channel EEGs (F7-Fpz, F8-Fpz, A1-Fpz, A2-Fpz). Median power spectra were estimated from 60 consecutive 2-sec EEG epochs collected during a resting period with closed eyes. Relative theta power (i.e., 4-8Hz power/ 2-20Hz power) was averaged over the 2 frontal channels (F7-Fpz, F8-Fpz). In addition, relative theta and alpha (8-12Hz) powers were calculated for each channel for retrospective, exploratory analyses.

Results: 21 subjects (58.3%) were antidepressant treatment responders (HAM-D reduction >/= 50%). As in previous studies, frontal theta activity decreased from baseline (21.2%) to week 1 (18.7%) in treatment responders, but not in treatment non-responders (23.4% at baseline and 25.9% at week 1). At one week relative theta power was statistically significantly lower in treatment responders versus non-responders ($p < 0.001$, see figure), predicting response with 83% accuracy (76% sensitivity, 93% specificity) and 0.88 Area Under the Receiver Operating Curve (AUROC). Relative theta power at one week correlated with the percent improvement in HAM-D ($R=-0.498$, $p=0.002$), indicating that subjects with lower relative theta power had greater improvement in mood by the end of the study. Retrospective analyses identified a 3-parameter model (utilizing relative theta power at 1 week, percent change from baseline in relative theta power, and baseline left-right asymmetry of combined theta+alpha power) that yielded improved performance (0.91 AUROC).

Conclusion: This prospective evaluation demonstrated that relative theta power measured after 1 week of medication predicts response to open-label, flexible dose treatment with SSRIs in MDD. The additional use of the change in EEG from baseline and an EEG asymmetry metric improved prediction in a retrospective analysis. It may be possible to develop an easy-to-use, clinical assessment tool using automated analysis of frontal EEG to predict treatment efficacy early in the course of antidepressant treatment.

Source(s) of Funding: This research was supported by Aspect Medical Systems, Inc.

POSTER NO. 171

THE RELATIONSHIP BETWEEN EARLY CHANGES IN THE HAMD-17 ANXIETY/SOMATIZATION FACTOR ITEMS AND TREATMENT OUTCOME AMONG DEPRESSED OUTPATIENTS

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Objective/Background: The HAM-D-17 Anxiety/Somatization factor includes six items: Anxiety (psychic), Anxiety (somatic), Somatic Symptoms (G.I.), Somatic Symptoms (general), Hypochondriasis, and Insight. This study examines the relationship between early changes (defined as baseline to week 1) in these HAM-D-17 Anxiety/Somatization Factor items and treatment outcome among major depressive disorder (MDD) patients participating in a study comparing the antidepressant efficacy of a standardized extract of hypericum with both placebo and fluoxetine.

Methods: Following a 1-week, single-blind wash-out, patients with MDD diagnosed by the Structured Clinical Interview for DSM-IV (SCID) were randomized to 12 weeks of double-blind treatment with hypericum extract (900 mg/day), fluoxetine (20 mg/day), or placebo. The 17-item Hamilton Rating Scale for Depression (HAM-D-17) was the primary efficacy measure. The ability of early changes in HAM-D-17 anxiety/somatization factor items to predict treatment outcome were assessed separately for patients who received active treatment (hypericum or fluoxetine) versus placebo with a logistic regression method.

Results: 135 patients (57% women, mean age = 37.3 + 11.0; mean baseline HAM-D-17 = 19.7 +3.2) were randomized to double-blind treatment and were included in the intent-to-treat analyses. The remission rates were 38% in the hypericum group, 30% in the fluoxetine group, and 21% in the placebo group. After adjusting for baseline HAM-D-17 scores and for multiple comparisons with the Bonferroni correction, patients who remitted (HAM-D-17 <8) after active treatment had significantly greater improvement in Somatic Symptoms (General) scores than non-remitters. No other significant differences in early changes were noted for the remaining items between remitters versus non-remitters who received active treatment. For patients treated with placebo, early change was not predictive of remission for any of the items.

Conclusion: The presence of early improvement on the HAM-D-17 item concerning fatigue and general somatic symptoms was significantly predictive of achieving remission at endpoint with active treatment but not with placebo.

Source(s) of Funding: This study was supported by NIMH (1 R10 MH56067-01A1)

POSTER NO. 172

PATIENT SATISFACTION WITH PHYSICIAN USE OF A COMPUTER-BASED CLINICAL DECISION SUPPORT SYSTEM(CDSS) DURING TREATMENT FOR A PSYCHIATRIC DISORDER

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Objective/Background: The aim of this study is to examine patients' acceptability of the use of CompTMAP (a CDSS for the treatment of psychiatric disorders) during treatment visits to improve care for outpatients.

Background: CDSSs are being developed to enhance physician adherence to treatment guidelines as well as improving patient outcomes. Little research has been conducted to evaluate patients' acceptance of these systems.

Methods: As part of a program to evaluate the effects of implementation of the CompTMAP system in a public mental health center (Harris county), over a 2-week period all patients were approached and asked to answer two questionnaires. Eighty-five patients agreed to complete a general questionnaire about their attitudes towards computers in general. Seventy-three patients who had been seen at least once by a physician using the CompTMAP system also agreed to complete a second questionnaire that evaluated the impact of this system on their care. The general computer attitudes questionnaire consists of eight general statements about computers and their use in society. The impact on treatment questionnaire contains eight statements that focus on how the use of a CDSS impacts their treatment. All items on both questionnaires are rated on seven point scales. Patient met current Axis I diagnosis of Major depressive disorder, Bipolar disorder, Schizophrenia or Schizoaffective disorder.

Results: Overall, the ratings were positive on both questionnaires with all mean ratings being above the midpoint of the scale for both questionnaires. A series of one-way ANOVAs were conducted to test for differences between diagnosis, gender, and race/ethic group on their general attitudes and impact on care questionnaires. A marginal effect for diagnostic groups in their perceptions of the impact on care being provided by their physicians using computers, with schizophrenics being less comfortable than the depressed and bipolar patients. There was also a marginal effect for race/ethic group, with African Americans being less comfortable with the use of computers in general then the other racial/ethic group. No other differences were found.

Conclusion: Regardless of diagnostic group, race and gender patients feel fairly comfortable with the care being provided by their physicians using a CDSS.

Source(s) of Funding: Funded in part by NIMH 1-R01-MH064062-01A2 (Madhukar H. Trivedi) and the Brown Foundation

POSTER NO. 173

MODAFINIL AS ANTIDEPRESSANT AUGMENTATION THERAPY IN MAJOR DEPRESSIVE DISORDER (MDD)

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Objective/Background: Major depressive disorder (MDD) is a highly prevalent and disabling medical condition. It has been estimated that between 29% to 46% of depressed patients show only partial or no response to treatment after a single antidepressant trial, and, even among responders, residual symptoms are rather common. Sleepiness and fatigue, commonly reported symptoms of MDD, may persist as residual symptoms despite adequate antidepressant therapy. This multicenter, double-blind, placebo-controlled study evaluated the efficacy of modafinil as an antidepressant augmenting agent for MDD patients who had not achieved remission and who had complained of symptoms of fatigue and excessive sleepiness despite adequate selective serotonin reuptake inhibitor (SSRI) treatment.

Methods: MDD patients (18-65 years) who were partial and non-responders to an adequate course of SSRI monotherapy (8 weeks) and on a stable SSRI dose (4 weeks) who had a screening/baseline 31-item Hamilton Depression Scale (HAM-D-31) score of 14-26 (inclusive), Epworth Sleepiness Scale (ESS) score 10, and Fatigue Severity Scale (FSS) score 4 were eligible. Patients were randomized to modafinil 200 mg/day or placebo for 8 weeks. Assessments included the Clinical Global Impression of Improvement (CGI-I), HAM-D-31, HAM-D-17, ESS, FSS, and Brief Fatigue Inventory (BFI).

Results: Of the 311 patients randomized, 135 modafinil-treated and 130 placebo-treated patients completed the study. The distribution of CGI-I scores at endpoint was significantly different for the modafinil and placebo groups, with higher rates of improvement observed among modafinil-treated patients ($p=0.02$); specifically, 64 (41%) of the modafinil-treated patients were either much or very much improved compared with 48 (32%) of placebo-treated patients, ($p<0.09$).There was a trend toward greater mean reductions in HAM-D-31, HAM-D-17, and ESS at endpoint (modafinil vs placebo, p 0.08). At endpoint, modafinil significantly reduced mean BFI worst scores ($p<0.05$ vs placebo); no statistically significant differences were found in FSS and BFI total scores. The most commonly reported adverse events were headache (13% modafinil; 16% placebo), nausea (9%; 2%), dizziness (7%; 2%), and dry mouth (6%; 3%).

Conclusion: The findings of this study suggest that modafinil may be a safe and effective augmenting agent for partial and nonresponders to SSRI treatment. Further studies of its efficacy in treatment-resistant depression are warranted.

Source of Funding: Cephalon, Inc., West Chester, PA

POSTER NO. 174

RELATIVE SENSITIVITY OF THE MONTGOMERY-ASBERG DEPRESSION RATING SCALE, THE HAMILTON DEPRESSION RATING SCALE, AND THE CLINICAL GLOBAL IMPRESSIONS RATING SCALE IN ANTIDEPRESSANT CLINICAL TRIALS

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Objective/Background: The Hamilton Depression rating scale (HAM-D) has become the standard tool in assessing the efficacy of new antidepressants. The alternative Montgomery-Asberg Depression Rating Scale (MADRS) has not achieved the level of acceptance as that of the HAM-D. However, its ease of use warrants evaluation as to whether it is comparable to HAM-D in its sensitivity in detecting antidepressant-placebo differences in antidepressant clinical trials.

Methods: A retrospective chart review was performed on the records of 346 depressed adult patients that participated in 15 randomized, placebo-controlled, double blind antidepressant clinical trials at the Northwest Clinical Research Center between 1995 and 2003. Independent samples t-tests were conducted to compare the mean baseline total HAM-D, MADRS, and CGI-S (Clinical Global Impressions Rating Scale for Severity) scores as well as the mean amount of change patients experienced between baseline and final visit. Additionally, we calculated effect sizes (measured as the mean change in rating scale scores with antidepressants minus the mean change for placebo divided by the placebo SD) for each of the three scales to compare treatment effect for patients assigned to placebo treatment or antidepressant treatment. Correlations were also conducted to examine the relationship between HAM-D and MADRS.

Results: The effect size was 0.71 with MADRS, 0.67 with CGI-S and 0.64 with HAM-D. A correlation analysis also revealed significant positive relationships between baseline MADRS and HAM-D ($r = 0.56$) and final MADRS and HAM-D for the total sample ($r = 0.91$), placebo group, and antidepressant group.

Conclusion: Our results suggest that HAM-D, MADRS, and CGI-S are similar in their sensitivity in detecting antidepressant efficacy in clinical trials. The correlational analysis indicated the HAM-D and MADRS were positively related to one another in the total sample, placebo, and antidepressant groups for baseline scores and final scores. Interestingly, the correlation coefficients between HAM-D and MADRS were higher at the end of trial compared to the beginning.

Source(s) of Funding: Northwest Clinical Research Center.

POSTER NO. 175

A DIRECT COMPARISON OF DEPRESSED PATIENTS FROM PRIMARY CARE VS. SPECIALTY CARE SETTINGS: PRELIMINARY RESULTS FROM STAR*D

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Objective/Background: No study has directly compared the clinical features of depression for patients entering clinical trials using identical enrollment criteria at both Primary Care (PC) and Specialty Care (SC) settings. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (www.star-d.org) provides a unique opportunity to provide such a comparison for patients with a major depressive disorder (MDD) requiring treatment. Our objective was to compare sociodemographic, course of illness, and clinical features of depression for patients concurrently enrolled in PC vs SC settings.

Methods: We report baseline data for the first 1500 patients enrolled in this ongoing trial. Patients were recruited from fourteen United States regional centers that were comprised of 41 clinic sites (19 PC, 22 SC). In this "hybrid" design trial, we used broadly inclusive eligibility criteria that required patients to have a DSM-IV diagnosis of nonpsychotic MDD; to not have had an unsatisfactory response to an adequate medication trial during their current episode; and to score 14 on the 17-item Hamilton Depression Rating Scale (HAM-D17). Primary measures at baseline included HAM-D17; 30-item Inventory of Depressive Symptomatology (IDS-C30); Cumulative Illness Rating Scale.

Results: SC and PC patients had equivalent degrees of depressive severity (HAM-D17 = 20; IDS-C30 = 36). SC patients were almost twice as likely to report a prior suicide attempt than PC patients (21% vs. 12%, $p<0.0001$). PC patients reported a significantly greater number and higher severity of general medical conditions. Besides suicide risk, the only distinguishing core symptom of depression was the greater likelihood of PC patients to endorse weight loss (29.7% vs 35.3%, $p=0.005$ by IDS-C30; 27.0% vs. 33.8%, $p=0.001$ by the HAM-D17).

Conclusion: Depressive severity was not different, and symptomatic presentations did not differ substantially. Major depressive disorder is more similar than different among patients at SC and PC settings. Thus, similar clinical and research methods to screen for, detect, and measure the effects of treatment can be applied in both settings.

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POSTER NO. 176

SEVERITY OF DEPRESSIVE SYMPTOMS AND RESPONSE TO ANTIDEPRESSANTS AND PLACEBO IN ANTIDEPRESSANT TRIALS

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Objective/Background: In a recent report (Khan et al., 2002) we noted that depressed patients with higher scores on the Hamilton Depression Rating Scale (HAM-D) showed a larger response to antidepressants compared to placebo. This preliminary report consisted of assessing response to antidepressants and placebo among 45 trials submitted to the FDA for the approval of new antidepressants. So, the severity of symptoms applied to the mean total HAM-D score for the entire population. In order to independently verify this phenomenon we conducted the current study. We assessed the role of severity of depressive symptoms using data from individual patients, rather than using data from the total sample. In this report, the study sample consisted of depressed outpatients who participated in phase II, phase III and phase IV trials at the Northwest Clinical Research Center (NWCRC).

Methods: We reviewed the data from 346 depressed adult patients that participated in 15 randomized, double blind, placebo-controlled antidepressant clinical trials at NWCRC between 1995 and 2003. The total 17-item HAM-D score prior to randomization was used to assess severity of depression. Based on patients' initial HAM-D scores, patients were sub-grouped to one of four severity of depression groups: low moderate, high moderate, moderately severe, and severe.

Results: The effect size (measured as the mean change in the total 17-item HAM-D score with antidepressants minus the mean change in the total 17-item HAM-D score with placebo divided by the placebo SD) was 0.56 in the low moderate group, 0.54 in the high moderate group, 0.68 in the moderately severe group, and 0.92 in the severe group. A correlation analysis revealed that in the group assigned to antidepressants, patients with more severe depression exhibit more change than less depressed patients. In the placebo group, a similar pattern was seen, but to a lesser extent and did not reach statistical significance.

Conclusion: The results of this study suggest that antidepressant-placebo differences may be larger among those depressed outpatients with higher pre-randomization HAM-D scores compared to those depressed outpatients with lower pre-randomization scores.

Source(s) of Funding: Northwest Clinical Research Center.

POSTER NO. 177

DOES SMOKING INHIBIT PLACEBO RESPONSE? A RETROSPECTIVE ANALYSIS OF THE EFFECTS OF SMOKING STATUS IN DEPRESSION CLINICAL TRIALS

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Objective/Background: It has been proposed (Harvey and Horst, NCDEU 2003) that smokers respond less well to antidepressants than nonsmokers. We sought to investigate this hypothesis by a retrospective analysis of pooled data from several placebo-controlled antidepressant studies.

Methods: Data from eight placebo-controlled outpatient antidepressant clinical trials were examined, representing a total of 2854 patients (808 smokers, 2046 nonsmokers). Smoking status was determined for each patient at study entry by history taking. The protocol-specified post-randomization double-blind treatment periods for these studies ranged from 6 to 10 weeks. Baseline-to-endpoint changes in HAMD17 total were analyzed by treatment (active drug vs. placebo) and smoking status. Active drugs included selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, and tricyclic antidepressants. Response rates of smokers and non-smokers were also compared, with response defined as a 50% reduction in HAMD17 total score. Rates of completion of double-blind treatment periods (versus early discontinuation) from the trials were examined as well.

Results: Smokers and nonsmokers showed similar changes in severity measures when treated with active comparators, but smokers showed smaller changes when treated with placebo than nonsmokers ($p = .020$). Despite this, response rates did not differ between smokers (45.5%) and nonsmokers (43.2%). Smokers were less likely (61.9%) to complete studies than nonsmokers (68.8%).

Conclusion: Smokers and nonsmokers respond similarly to antidepressants, but smokers may be more resistant to placebo effects. Smoking status should be routinely determined and reported on in depression clinical trials. It may help explain why some patients respond better to placebo than others, or why differences between active drugs and placebo are more apparent in some clinical trials than in others.

Source(s) of Funding: Eli Lilly and Company

POSTER NO. 178

ASSESSMENT OF ANHEDONIA IN DEPRESSED AND IN HEALTHY INDIVIDUALS EXAMINING THE VALIDITY OF THE SNAITH-HAMILTON PLEASURE SCALE

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Background & Significance: Anhedonia is a diminished capacity or the inability to experience pleasure. Historically, it was initially viewed as a trait and a state marker in schizophrenic disorders and less so in depression. Anhedonia is now primarily viewed as a key symptom of depression.

The earlier absence of focus on anhedonia in depression was reflected in its absence from major rating instruments of depression, i.e. the Hamilton Depression Rating and Beck Depression Inventory. Since the inclusion of anhedonia for the diagnosis of depression in DSM-IIIR, there is a renewed interest. Hedonic tone is being explored as a biological marker for mood disorders and for that reason it becomes increasingly important to correctly assess and quantify this symptom. The Inventory for Depressive Symptomatology (IDS) includes items that are related to the assessment of anhedonia. Several pleasure/hedonic capacity scales have been devised such as the ones by Chapman et al, Fawcett et al, and Kazdin. They have been criticized for their length, cultural or age bias, and inclusion of exotic items. Snaith et al devised a measure of anhedonia, the Snaith-Hamilton Pleasure Scale (SHAPS) that has remained largely underutilized since its development in 1995.

Objectives: To validate SHAPS as a measure of hedonic tone by investigating the following in both unipolar and bipolar depressive states as well as in subjects free of known psychopathology:

a. The correlation between SHAPS and IDS "anhedonia" items 8, 19, 21, 22.
b. The correlation between SHAPS and other known measures of hedonic states, i.e Chapman's social and physical anhedonia and Clark-Fawcett's pleasure scale.

Method:

Instruments:

- Snaith-Hamilton Pleasure Scale (SHAPS). Self-administered. 14 items.
- Chapman Scales of Physical and Social Anhedonia. Self-administered. 114 items.
- Fawcett-Clark Pleasure Scale. Self-administered. 36 items
- Inventory for Depressive Symptomatology. Self -rated version. 30 items.

Subjects:

N= 24, 13 females,
Age Range= 23-50
Diagnosis=11 healthy, 9 unipolar depression, 3 bipolar depression

Procedures:

The above self-rated scales were administered to consecutive adult patients participating in mood disorder protocols and in healthy controls. Three measures of hedonic tone were given in random order so that eventually similar numbers of all possible six orders of presentation were obtained.

Results: Preliminary results indicate that SHAPS is significantly correlated with Chapman's measures of Physical and Social anhedonia (.62, .67 respectively), with the Fawcett-Clark pleasure Scale (-.48) and with IDS items 8 (.63), 19 (.71), 21 (.71), and 22 (.54). These results are promising in that the SHAPS is easy to use and is emerging as a valid, meaningful, and relevant measure of anhedonia.

POSTER NO. 179

SENSITIVITY TO TREATMENT DIFFERENCES IN HIGH ENTRY SCORE VERSUS LOW ENTRY SCORE SUBGROUPS IN DEPRESSION CLINICAL TRIALS

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Objective/Background: In order to investigate whether restricting attention to data from more severely depressed patients within a clinical trial is likely to increase the ability to separate active drug from placebo, we examined treatment differences in patients whose entry scores were above the median, patients whose entry scores were below the median, and all patients.

Methods: Data from a total of 4616 patients in 19 placebo-controlled, outpatient antidepressant clinical trials were analyzed. Active drugs included selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, and tricyclic antidepressants. For each trial, the median HAMD17 score and Maier subscale score at entry were calculated, and for each measure, subgroups were defined containing above-median-score patients, below-median-score patients, and all patients. For each trial and subgroup, an effect size was calculated for the treatment difference in baseline-to-endpoint change between active drug and placebo using linear regression. Weighted averages of overall statistics across trials were calculated using the number of patients per study as the weighting factor.

Results: An analysis of the HAMD17 totals showed that, in 14 of 19 trials (74%), active vs. placebo treatment difference p-values were smaller in all patients than in above-median subgroups, and in 11 of 19 trials (58%), below-median subgroups showed smaller p-values than above-median subgroups. In only 9 of 19 trials (47%) was active vs. placebo treatment difference effect size larger in the above-median subgroup than in all patients. Similar results were seen when the Maier subscale was used to define the subgroups. Overall average active vs. placebo p-value was smallest in all patients and overall average active vs. placebo effect size was largest in the below-median subgroup for both HAMD17 and Maier. Our results may be explained by greater outcome variation in more severely depressed patients. Active vs. placebo difference in mean baseline-to-endpoint change was generally largest in above-median subgroups, but standard deviation of baseline-to-endpoint change was also generally highest in above-median subgroups.

Conclusion: Discrimination between active drug and placebo in outpatient depression trials is not improved by restricting attention to more severely depressed patients.

Source(s) of Funding: Eli Lilly and Company

POSTER NO. 180

ASSESSING DEPRESSION: HOW MUCH TIME AND EFFORT DOES IT TAKE VIA INTERACTIVE VOICE RESPONSE (IVR)?

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Introduction: The durations of interviews in which clinicians assess patients with the Hamilton Depression Rating Scale (HAMD) have been reported to vary widely and may be related to the quality of the ratings obtained. Interview duration should also relate to depressive severity, as additional probe questions are needed to determine accurate severity ratings. The durations of interactions in which IVR systems assess patients with the HAMD also vary considerably and may relate to data quality and depressive severity.

Methods: The duration of patient IVR interactions, question response times, and self-reported HAMD severity were analyzed from three large placebo-controlled multi-center antidepressant clinical trials. The data from the studies were pooled, providing 5,373 IVR HAMDs from 775 unique ID numbers. Clinician HAMDs (3,385) obtained within 2 days of an IVR HAMD from 605 unique patients were compared for outcome convergence.

Results: The mean (Standard Deviation) time for patients to complete the 5,373 IVR HAMDs was 7.11 1.78 minutes, ranging from 1.77 to 17.88 minutes. On average, 43.31 6.60 questions were asked (range 29 to 61), and the mean IVR 17-item HAMD score was 15.22 7.63 (range 0 to 43). HAMD scores correlated with the number of questions asked ($r = .941$), assessment completion time ($r = .661$), number of prior calls completed ($r = -.425$), and the mean response time to each question ($r = .152$). The mean response time across all 232,680 questions asked was 8.8 4.3 seconds (range 0 to 76 seconds). Response times to individual questions correlate with the number of response options ($r = .328$), number of previous questions during the assessment ($r = .136$), number of prior calls completed ($r = -.123$), and IVR total HAMD score ($r = .059$). The correlation between the 17-item total scores of the 3,385 time-matched IVR and clinician HAMD scores was .787. All p-values of reported correlations are $< .001$.

Conclusion: The time required to obtain patients' self-reports relates strongly to the self-reported severity. Self-reported severity correlates well with clinician-assessed severity. Similar research should be explored with respect to clinical interviews. While precise timing of interactions during an interview would be disruptive, routine recording of interview start and stop times would be an initial step worth taking. Finer-grained measurement of the temporal aspects of clinical interviews via videotape may also provide a valuable source of information about data quality and current collection processes in clinical trials.

Sources of Funding: Eli Lilly and Company, Healthcare Technology Systems

POSTER NO. 181

BODILY PAIN IN OLDER PRIMARY CARE PATIENTS WITH DEPRESSION

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Background: Pain and depression are often diagnosed and treated concurrently by primary care (PC) physicians. Pain and depression have been shown to be mutually exacerbating, and have significant effects on both quality of life and health service utilization. When tricyclic antidepressants, which have analgesic properties, were first line treatment for affective disorders, there was a great interest in the treatment of pain by psychiatrists. SSRI's, now first line treatment, have not been consistently shown to provide analgesia, and the interest by psychiatrists in the treatment of pain during the 1980's and 1990's waned. However, since the release of serotonin and norepinephrine reuptake inhibitors (SNRI's), there has been a revived interest by our field in the relationship between these two disorders. This analysis is focused on the influence of reported pain on treatment response in late life depression.
Objective: To determine if the degree of reported bodily pain affected treatment response in elderly primary care patients being treated for depression.
Methods: The subjects reported in this study were enrolled in the Pittsburgh site (n=128) of the Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT)1. This multicenter trial was designed to test the impact of a primary care-based intervention on reducing the two major risk factors for suicide in late life: suicidal ideation and depression. Subjects were older adults (> 60 years of age) being treated for depression in PC. Treatment was either: 1) standard depression treatment provided by a PCP, or 2) depression management with a "health specialist" (HS). Response to treatment was evaluated at both transition to continuation at 4 months, and at 12 months. For both of these time points, a sustained response was defined by a HRSD-24 < 10. Bodily pain was assessed with the SF-16 bodily pain index (BPI); higher scores suggest less pain.
Results: Forty-seven of the Pittsburgh Ss received usual care, and 81 were treated by the HS. Using an Intent to Treat (ITT) analysis of the 81 subjects in the HS group only, we compared baseline bodily pain scores in the 61 responders and the 20 non-responders. Response was defined as those who made transition to continuation treatment at 4 months. The responders had lower baseline bodily pain than the non-responders. The mean BPI score for responders was 72.5 ($\pm$30.5) versus 51.2 ($\pm$31.91) for the non-responders (Wilcoxon Exact p = 0.009). Using all of the subjects in both treatment groups, we used a completer analysis to examine subjects who had scores at both baseline and 12 months. There were 79 total subjects: 31 (39%) received usual care and 48 patients were treated by the HS. At 12 months, subjects who maintained a treatment response reported less bodily pain (BPI = 75 [SD = 30.8]) than subjects with a HRSD-24 > 10 (BPI = 60.4 [SD = 33.7]), Wilcoxon Exact p = 0.05. At baseline, a similar trend was also found between these two groups, with those patients who sustained a treatment response at 12 months reporting less bodily pain at baseline (Wilcoxon Exact p = 0.074).

Conclusions: Patients who report less bodily pain at either baseline or at 12 months may be more likely to both respond and to remit to antidepressant treatment in the PC setting.

1. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: A randomized controlled trial. Bruce ML, Ten Have TR, Reynolds CF, Katz II, Schulberg HC, Mulsant BH, Brown GK, McAvay GJ, Pearson JL, Alexopoulos GS. JAMA. 2004;291:1081-1091.

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POSTER NO. 182

COMPLETE SOMATIC SYMPTOM RESOLUTION WITH VENLAFAXINE OR SSRIS

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Objective: Patients with mild to moderate depression often experience somatic symptoms such as backaches, headache, muscle aches, loss of energy, fatigue, and heaviness in the limbs, back, or head. For many depressed patients, these symptoms are among the primary reasons for seeking treatment. Results of a previous pooled analysis suggested that the attainment of remission of overall depression symptoms with venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI), was significantly greater than that with the selective serotonin reuptake inhibitors (SSRIs) or placebo. The goal of this analysis of original data from 31 depression studies was to compare rates of complete resolution of somatic symptoms of depression with venlafaxine/venlafaxine extended release (XR), selective serotonin reuptake inhibitors (SSRIs), and placebo.

Methods: Data from 31 randomized, double-blind studies comparing treatment with venlafaxine/venlafaxine XR (n=3273), SSRIs (fluoxetine, paroxetine, sertraline, citalopram, or fluvoxamine; n=3217), or placebo (n=932) were pooled to evaluate the effect of treatment on somatic symptoms of depression. The proportion of patients reporting somatic symptom resolution after 8 weeks on the anxiety/somatization (A/S) factor ($\geq$50% reduction in baseline A/S score) of the HAM-D_{21} scale (anxiety-psychic, anxiety-somatic, somatic symptoms-gastrointestinal, somatic symptoms-general, hypochondriasis, and insight) was compared. Complete somatic symptom resolution (item score=0) was compared for the somatic symptoms general and gastrointestinal items. Pairwise comparisons between groups were performed using the Fisher exact test.

Results: Somatic symptom resolution on the A/S factor was achieved by 58% (1910/3273) of the venlafaxine/venlafaxine XR group, 53% of SSRI-treated patients (1714/3216), and 41% (378/932) of placebo patients. Somatic-general complete symptom resolution was achieved by 38% (1255/3273) of the venlafaxine/venlafaxine XR group, 32% (1033/3217) of SSRIs-treated patients, and 24% (228/932) of placebo patients. All comparisons were statistically significant ($P<0.001$). Complete symptomatic resolution on the somatic-gastrointestinal item was achieved by 66% (2170/3273) of venlafaxine/venlafaxine XR-treated patients, 63% (2026/3216) of the SSRI group, and 70% (657/932) of the placebo group ($P=0.005$ venlafaxine vs SSRI; $P=0.016$ venlafaxine vs placebo; $P\leq0.001$ SSRI vs placebo).

Conclusion: These results demonstrate that treatment with venlafaxine/venlafaxine XR is significantly more effective than SSRIs in producing complete resolution of somatic symptoms of depression.

Funding Source: Wyeth Research

POSTER NO. 183

RESEARCH DESIGN FEATURES AND PATIENT CHARACTERISTICS RELATED TO ANTIDEPRESSANT CLINICAL TRIAL OUTCOME

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Objective/Background: In over half of recent antidepressant clinical trials, approved antidepressants fail to show an advantage over placebo. Evidence suggests that response to placebo is increasing (Walsh et al., 2002). This increase in response to placebo may be related to other factors such as severity of mood symptoms at baseline (Khan et al., 2001), use of a fixed or flexible dose regimen (Khan et al., 2003), trial length (Khan et al., 2000), or number of treatment arms (Zimmerman et al., 2003). We examined which, if any, research design features and patient characteristics would be significantly different among successful (greater antidepressant-placebo difference) antidepressant trials versus unsuccessful ones (smaller antidepressant-placebo difference).

Methods: We reviewed clinical trial data for 9 antidepressants approved by the Food and Drug Administration (FDA) between 1985 and 2000. From these 9 antidepressant research programs, 52 clinical trials were included in the study. Antidepressant-placebo differences on mean total HAM-D scores were used to assess the successfulness of the antidepressant trial.

Results: We evaluated both antidepressant trial design features and patient characteristics and found 9 trial design features and patient characteristics that were present in all 9 of the antidepressant research programs. Use of flexible dose was twice as likely to lead to a positive result compared to fixed usage. The more positive trials were associated with higher number of male depressed patients. The most successful trials had the fewest treatment arms. Lastly, the mean total HAM-D scores were higher among more successful trials compared to less successful trials. Duration of antidepressant trial, number of patients per treatment arm, number of sites, and age of the patients was similar among both successful (greater antidepressant-placebo difference) and less successful (smaller antidepressant-placebo difference) trials.

Conclusion: These findings may help in the design of future antidepressant trials.

Source(s) of Funding: Northwest Clinical Research Center.

POSTER NO. 184

STAR*D SAFETY MONITORING: LESSONS FROM A LARGE HYBRID STUDY OF DEPRESSION

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National Institute of Mental Health guidelines to manage suicidality in clinical trials suggest a full range of procedures to minimize suicidal risk, yet no reports to date have shown how these suggestions are operationalized. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) is a study in representative participant groups and settings, across 14 regional centers and more than 30 clinical sites that used the NIMH guidelines as a template to manage suicidal risk. Patients who present for care to either their primary care physician or psychiatrist are invited to participate if antidepressant treatment is appropriate. Open treatment is provided to patients with a flexible algorithm that uses equipoise randomization. Outcomes are assessed by a single blind rater and include clinical outcomes (e.g., symptoms, function, side effect burden, client satisfaction) and health care utilization and cost estimates. Because of the large size of the study (N=4000), the wide geographic distribution, the large number of treating STAR*D clinicians, the broad array of psychiatric and medical comorbidities, and the complexity of the treatment algorithm, the risk of suicide coupled with the focus on treatment resistant depression, safety monitoring presented a unique challenge. This poster will describe the NIMH-derived methods used to manage suicidal risk in STAR*D including the use of an interactive voice recognition response system to alert clinicians, regional center directors, and safety officers.

POSTER NO. 185

A COMPARISON OF FACE-TO-FACE AND REMOTE ADMINISTRATION OF THE HAMILTON DEPRESSION RATING SCALE VIA VIDEOCONFERENCING

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Objective/Background: Use of remote, centralized raters in clinical trials who are well-trained and highly calibrated with each other has the potential advantage of achieving a higher degree of inter-rater reliability than is attained by current methodology with large numbers of raters at diverse sites. They also afford the advantage of being blinded to study entrance requirements and visit number, thus minimizing these potential sources of rater bias. Before remote assessments can be utilized, it needs to be determined whether interviews conducted remotely using videoconferencing are equivalent to interviews conducted in the traditional face-to-face manner, i.e., whether mode of administration affects the psychometric properties of the scale.

Methods: 42 Subjects with a mood disorder were administered two HAMD interviews by two independent interviewers. In cohort 1 (n=21) , each subject received one face-to-face and one remote (videoconference) HAMD. In cohort 2 (n=21), each subject received two face-to-face HAMDs. Order and cohorts were counterbalanced. Interviewers were blind to the results of the other rater's interview. All subjects had a mood disorder according to DSM-IV (major depression (n=28), minor depression (n=1), depression in partial remission (n=7), bipolar disorder-depressed (n=4), depression NOS (n=1), or bipolar disorder NOS (n=1)). Inclusion of all mood disorders enabled evaluation of equivalence across a wide range of severities.

Results: The mean scores obtained by HAMDs conducted remotely by videoconference and HAMDs conducted face to face were almost identical (18.38 vs 18.23 respectively, mean difference = 0.15 points), $t(20)=0.234$, $p = .817$. The inter-rater reliability (intraclass correlation; ICC) was $r=.88$, $p<0001$, 95% C.I. .7372, .9503. Similarly, the ICC between the 20 pairs of interviews where both were conducted face to face was $r=.93$, $p<.0001$, 95% C.I. .8401, .9711. The inter-rater reliability (ICC) between face-to-face and remote interviews was not significantly different from two interviews done face to face, $z=0.85$, $p = .198$, 95% confidence interval for the difference ($d(r)=.05$) = -0.7333, 0.3546. Similar levels of internal consistency (coefficient alpha) were found for both versions ($r= .74$ for videoconferencing, $r=.77$ for face-to-face administration).

Conclusion: Results support the psychometric equivalence of HAMD interviews conducted remotely via videoconferencing to those conducted face-to-face. Whether remote, centralized ratings conducted by blinded raters improve signal detection compared to traditional face-to-face ratings is yet to be determined. A pilot study comparing remotely conducted HAMD's to face-to-face administration in a clinical trial context is currently underway and will examine this issue.

Source(s) of Funding: This study was supported by funds from MedAvante, Inc.

POSTER NO. 186

COMPARATIVE EFFICACY OF SERTRALINE AND VENLAFAXINE-XR IN MAJOR DEPRESSION

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Objective: To compare the efficacy of sertraline versus venlafaxine-XR in Major Depressive Disorder (MDD) on measures of quality of life (primary endpoint: Quality of Life Enjoyment & Satisfaction Questionnaire, Q-LES-Q) as well as on traditional depression outcomes.

Methods: This study was an international, 8-week, double-blind study of 163 outpatients with DSM-IV MDD (69% female; mean age, 37; mean baseline HAM-D, 23) who were randomised to sertraline (50-150 mg/day; n=79) or venlafaxine-XR (75-225 mg/day; n=84), followed by a 2-week taper period. The primary efficacy endpoint was quality of life, measured by the (Q-LES-Q). Secondary efficacy measures included HAM-D and CGI scales. Response was defined as a $\geq$50% reduction in HAM-D; remission was defined as HAM-D$\leq$7. Intent-to-treat (ITT) analyses were undertaken at week 8 with the last observation carried forward (LOCF), and were repeated at week 8 amongst completers. Of the 163 patients, 74% had Q-LES-Q (n=120) and HAM-D (n=121) assessments available at week 8, and were included in the week-8 completer analyses. Changes from baseline scores were analysed using analysis of covariance; least-square (LS) means and p-values are presented. The Cochran-Mantel-Haenszel test was used to produce p-values for differences in response and remission rates between groups.

Results: LS mean change from baseline in Q-LES-Q was comparable between sertraline and venlafaxine-XR treatments for both week-8/LOCF (16.8$\pm$1.8 vs. 17.5$\pm$1.8; p=0.74) and week-8 completer (19.9$\pm$1.8 vs. 19.5$\pm$1.8; p=0.86) analyses. Similarly, sertraline and venlafaxine-XR resulted in a comparable reduction in HAM-D total scores; week-8/LOCF (-15.9$\pm$1.0 vs. -14.3$\pm$0.9; p=0.17), week-8 completer (-17.6$\pm$0.8 vs. -16.1$\pm$0.8; p=0.15). Sertraline and venlafaxine-XR had similar response rates; week-8/LOCF (71% vs. 71%; p=0.95), week-8 completers (81% vs. 85%; p=0.35). Likewise, remission rates were similar for both treatments; week-8/LOCF (60% vs. 54%; p=0.47), week-8 completers (71% vs. 63%; p=0.44). Anxiety symptoms had responded ($\geq$50% reduction in HAM-D anxiety-somatization factor) at week-8/LOCF in 76% of sertraline and 70% of venlafaxine-XR patients (p=0.30), and in 87% of sertraline and 81% of venlafaxine-XR week-8 completers (p=0.41).

Conclusion: Sertraline and venlafaxine-XR were found to produce similar effects on quality of life, and have comparable antidepressant efficacy in patients with moderate-to-severe MDD.

POSTER NO. 187

MAINTENANCE TREATMENT WITH ESCITALOPRAM PREVENTS RECURRENCE OF DEPRESSIVE EPISODES

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Objective/Background: Depression is often a recurrent condition, though recurrence is preventable with maintenance antidepressant treatment. Escitalopram is an effective and well tolerated SSRI antidepressant; continuation treatment with escitalopram has been shown to prevent relapse of a depressive episode.

Methods: Patients with recurrent major depression (at least 2 previous episodes; baseline MADRS >= 22) who have responded (MADRS score of 12 or less) to SSRI treatment in a lead-in trial received 16 weeks of flexible dose open-label escitalopram (10 - 20 mg/day) treatment. At the end of the open-label phase, patients with MADRS <= 12 were randomized to 52 weeks of fixed dose double-blind treatment with escitalopram (10 or 20 mg/day) or placebo. Recurrence was defined as MADRS >= 22 or insufficient therapeutic response during the double-blind phase.

Results: A total of 203 patients received at least one dose of double-blind phase treatment. Cumulative recurrence rates were 30% for the escitalopram group and 62% for the placebo group (hazard ratio = 0.30; $p<0.001$). Crude recurrence rates were 26% for the escitalopram group and 53% for the placebo group ($p<0.001$). Long-term escitalopram treatment was well tolerated, with rates of discontinuation due to adverse events of 3.9%.

Conclusion: Maintenance treatment with escitalopram is well tolerated and significantly reduces the risk for recurrence of depressive episodes.

Source(s) of Funding: Forest Labs

POSTER NO. 188

COMPARATIVE EFFICACY OF SERTRALINE VERSUS VENLAFAXINE-XR IN ANXIOUS-DEPRESSION

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Objective: To compare the efficacy of sertraline versus venlafaxine-XR in a subgroup of depressed patients with anxious-depression.

Methods: An international, 8-week, double-blind study of 163 adult outpatients with Major Depressive Disorder (MDD) who were randomised to sertraline (50-150 mg/day; n=79) or venlafaxine-XR (75-225 mg/day; n=84), followed by a 2-week taper period. The anxious-depression subgroup was defined by a baseline HAM-D anxiety-somatization score≥7. Response was defined as a ≥50% reduction in HAM-D; remission was defined as HAM-D≤7. Intent-to-treat (ITT) analyses were performed at week 8 with the last observation carried forward (LOCF), and repeated at week 8 amongst completers. Changes from baseline scores were assessed using analysis of covariance; least-square (LS) means and p-values are presented. The Cochran-Mantel-Haenszel test was used to determine p-values for differences in response and remission rates between groups.

Results: One hundred and twenty (74%) of 163 outpatients met criteria for MDD, anxious subtype (73% female; mean age, 36 years; mean HAM-D, 25). Of the 120 patients, 73% (n=88) had a HAM-D assessment available at week 8, and were included in the week-8 completer analyses. In the anxious-depressive subgroup, sertraline was comparable to venlafaxine-XR for LS mean change from baseline in HAM-D total scores at week-8/LOCF (-17.3 ±1.1 vs. -14.8±1.0; p=0.07), and for week-8 completer analyses (-18.7±1.0 vs. -16.6±1.1; p=0.11). Sertraline and venlafaxine-XR showed similar HAM-D response rates for both week-8/LOCF (80% vs. 69%; p=0.26), and for week-8 completer analyses (86% vs. 82%; p=0.77). Similarly, HAM-D remission rates were comparable for both treatments at week-8/LOCF (63% vs. 54%; p=0.44), and for week-8 completers (73% vs. 61%; p=0.39). Anxiety symptoms had responded (=50% reduction in anxiety-somatization factor) in 83% of sertraline and 71% of venlafaxine-XR patients at week-8/LOCF (p=0.12), and in 93% of sertraline and 82% of venlafaxine-XR patients for week 8 completers analyses (p=0.14). Regarding the total sample (n=163), no significant differences were found between treatments on these outcome measures.

Conclusion: Sertraline and venlafaxine-XR were found to have similar antidepressant efficacy in anxious-depression, a common clinical subtype of MDD.

Source of Funding: Pfizer Pty Limited.

POSTER NO. 189

RESULTS FROM THE ARISE-RD (AUGMENTATION WITH RISPERIDONE IN RESISTANT DEPRESSION) TRIAL

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Objective/Background: Nearly 40% of patients with major depression fail to respond adequately to available antidepressants. Preliminary results from ARISe-RD, an ongoing trial evaluating risperidone augmentation in resistant depression, suggest this is an effective strategy.

Methods: Patients historically failing = 1 antidepressant, plus a prospective 4-6 week citalopram course, received 4-6 weeks of open-label risperidone augmentation (0.25-2 mg/day). Patients who remitted after augmentation continued in a 6-month double-blind placebo-controlled relapse prevention phase.

Results: Of the 502 subjects, 88.8% did not respond (=50% HAM-D reduction) to citalopram monotherapy. During risperidone augmentation (N = 386), mean (± SD) total scores improved significantly from baseline to endpoint on HAM-D (-11.1 ± 6.9; p<.0001), MADRS (-14.5 ± 9.6; p<.0001), CGI-S (-1.7 ± 1.2; p<.0001), and HAM-A (-7.8 ± 7.3; p<.0001). Moreover, remission (MADRS =12) rates were 59.3% at endpoint. Discontinuations due to adverse events were low (4.6%) and there were no significant changes in movement disorder ratings. Data from the double-blind relapse prevention phase will be available and presented.

Conclusion: These results from ARISe-RD, the largest trial of atypical antipsychotic augmentation in resistant depression, indicate that low-dose risperidone augmentation may provide safe, rapid, and robust improvement in depressive symptoms and associated anxiety. Positive results from the relapse prevention phase would suggest a role for risperidone augmentation for maintenance treatment in resistant depression.

Source(s) of Funding: Janssen Pharmaceutica Products, L.P.

POSTER NO. 190

APOE4 ALLELE INFLUENCES ANTIDEPRESSANTS' COGNITIVE EFFECTS IN THE ELDERLY

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Objective/Background: A recent investigation suggests that older depressed patients with the ApoE4 allele may respond quicker to mirtazapine than paroxetine. We investigated whether the ApoE4 allele impacts the effects of these antidepressant treatments on cognitive function.

Methods: A total of 255 clinically depressed, older patients were tested at baseline and again after eight weeks of treatment with paroxetine or mirtazapine. The cognitive battery included measures of global cognition (MMSE), visuospatial ability (BVRT), attention and inhibition response (Stroop), psychomotor speed (Finger Tapping), executive function (Trails B) and delayed verbal recall. Multiple regression analyses examined the effects on cognition of treatment received, the ApoE4 allele and controlled for age, gender and education.

Results: Overall, no significant positive cognitive changes were observed following antidepressant treatment. However, we observed positive effects of antidepressant treatment on cognition in patients with the ApoE4 allele which depended on type of treatment. Patients with the ApoE4 allele treated with paroxetine declined on the measure of attention and inhibition, while patients with the ApoE4 allele treated with mirtazapine did not decline. Patients with the ApoE4 allele in both treatment groups exhibited improvement in executive function. Independent of ApoE4 allele status, both treatment groups exhibited a significant decline in performance on visuospatial ability, but the Paroxetine group exhibited significantly greater decline on this measure.

Conclusion: These results suggest that older depressed patients with the ApoE4 allele experience some benefits on cognition of antidepressant medication and that treatment with mirtazapine is more protective of cognitive function, particularly in those patients with the ApoE4 allele.

Source(s) of Funding: Organon Pharmaceuticals USA

POSTER NO. 191

AN OPEN-LABEL, RATER BLINDED STUDY OF ARIPIPRAZOLE AS AN AUGMENTATION AGENT IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

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Objective: Aripiprazole is a novel atypical antipsychotic with partial agonist activity at D2 and 5HT1A receptors and antagonism at the 5HT2 receptors. This study examined the clinical utility and tolerability of aripiprazole as an augmenting agent in patients with treatment-resistant depression.

Methods: In an open-label, rater-blinded, prospective, study, 6 patients with major depression who had failed to respond to an adequate trial of at least one antidepressant were prescribed aripiprazole (dose 5-30 mg per day) for 6 weeks. The dose of pre-existing antidepressant remained unchanged during the study. Efficacy measures included: a) 50% or greater reduction in scores on the Hamilton Depression Rating Scale (HAMD) from baseline to end of treatment, b) decrease of 2 or more points from baseline to end of treatment on the Clinical Global Index severity (CGI-S) and improvement (CGI-I) ratings. Side effects were rated on the Simpson Angus Extrapyramidal Scale (SAES), the Barnes Akathisia Scale (BAS) and Systematic Assessment for Treatment Emergent side Effects (SAFTEE).

Results: The mean (S.D.) HAMD scores at baseline and end of treatment were 21.7 (9.19) and 8.00 (7.43) respectively. 5 out of 6 (83 %) were responders as defined by changes in HAMD, CGI-S and CGI-I scores. By end of second week the HAMD scores had reduced by 56 %. The mean daily dose of aripiprazole was 12.5 mg. No subjects dropped out of the study. The common side effects reported were akathisia/restlessness: 2 out of 6 (33%), nausea: 1 out of 6 (16%) and a mild tremor: 1 out of 6 (16 %).

Discussion/Conclusions: The study indicates the potential utility of aripiprazole as an augmenting agent in treatment resistant depression. Given the open-label design and the small sample size of the study, adequately powered, randomized, double-blind, placebo controlled trials are necessary to fully evaluate the role of aripiprazole in treatment resistant depression.

Funding: Investigator initiated through Bristol Myers Squibb.

POSTER NO. 192

ASSESSMENT OF ANTIDEPRESSANT EFFECTIVENESS IN THREE SUCCESSIVE TRIALS

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Objective/Background: The literature on antidepressant treatment suggests that the usual response rate is 50% and that the remission rate is approximately 25 to 35%. The salient issue is the accepted definition of adequate treatment. For depressive disorders, when comparing outcome among different treatment modalities, the usual convention is to look at outcome of a single antidepressant trial. This inadequately reflects the potential of antidepressant benefit. It is a pharmacologic dictum that after 6 to 8 weeks lack of improvement requires switching treatment. Good clinical practice suggests that this process should be repeated at least three times.

Methods: We reviewed two independent data sets. For the first dataset, we examined the outcome of a consecutive series of 170 patients. Patients who did not respond to their first antidepressant were treated with a second antidepressant, and those unresponsive to a second antidepressant were treated with a third antidepressant. For the second dataset, we reanalyzed data from a double-blind crossover study completed with first-generation antidepressants.

Results: In an intent-to-treat analysis, remission (defined as a Hamilton Depression Scale score of 7 or less) was 64% (N=170) of the patients in the first group and 65% (N=420) of patients in the second group. Contrast of these groups' SCL-90 depression factor scores with scores of a "well" community sample indicated that these patients were virtually free of depressive symptoms.

Conclusion: We think criteria in determining treatment outcome ought to include exposure to three successive treatments. We believe that a clearer estimate of remission rates is critical. This issue is widely discussed in newspapers, and public image suggests these drugs are "not so great." This issue has significant public health implications. If the public believes that antidepressants have a weak to modest effect, patients may be less likely to seek treatment. This may explain why many depressed patients are untreated.

Source(s) of Funding: Studies supported by Organon, Inc. 7-79492 to Dr. Frederic Quitkin, NIMH grant MH-56058 to Dr. Patrick McGrath, and NIMH grants MH39143 and MH35297 to Dr. Frederic Quitkin

POSTER NO. 193

DOUBLE-BLIND DOSE-FINDING STUDY OF DOCOSAHEXANOIC ACID (DHA) IN MAJOR DEPRESSIVE DISORDER

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Objective/Background: Recent evidence suggests effectiveness of omega-3 fatty acids for bipolar disorder, unipolar depression, and psychotic disorders, sometimes with doses as low as 1-2g/day. We undertook a pilot dose-finding study of docosahexanoic acid (DHA) to determine its dose/response relationship in the treatment of major depressive disorder (MDD).

Methods: We recruited thirty-four adults, ages 18-80 (47% women; mean age 42, SD=14), diagnosed with MDD by the Structured Clinical Interview for DSM-III-R, with a 17-item Hamilton-Depression Rating Scale (HAM-D-17) score of 18 or greater at entry. Subjects were randomized into three arms. The dosing was double blind. One group (n=14) received 1g/day of DHA for 12 weeks; the second group (n=10) received 2g/day of DHA; and a third group (n=10) received 4g/day of DHA. Subjects were administered a questionnaire about dietary habits, in particular about consumption of omega-3-rich foods, so as to control for any dietary influence on the response to the study medication. Outcome was measured by improvement in HAM-D-17, Beck Depression Inventory (BDI), and Clinical Global Impressions (CGI). Response was defined as 50% or greater decrease in HAM-D score.
Results: Among study completers, the group receiving 1g/day showed an 83% response rate; the group receiving 2g/day showed a 40% response rate; and the group receiving 4g/day showed a 0% response rate. Intent-to-treat (ITT) analysis showed a similar trend (45% response rate for 1g/day, 33% for 2g/day, and 14% for 4g/day). Among completers, the low and intermediate dose groups had a statistically significant improvement in HAM-D-17 scores ($p<0.05$); in the ITT sample, improvement in HAM-D-17 scores reached significance for all 3 groups ($p<0.05$). Although side effects were more common at higher DHA doses, there was no significant difference in dropouts due to side effects in the intermediate and higher dose groups.

Conclusion: DHA may work best at lower doses. At higher doses, we may be observing an "overcorrection effect" with regard to fatty acid imbalance. Further comparison between the different types of omega-3 fatty acids and placebo is needed, as well as investigation of the psychotropic mechanisms of action of the omega-3s.

Source(s) of Funding: NARSAD

POSTER NO. 194

A ONE-YEAR LONGITUDINAL STUDY OF VNS THERAPY IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

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Objective/Background: We report the results of an open-label long-term phase of VNS therapy in patients with treatment-resistant depression.

Methods: In the open-label long-term study, 110 patients in the treatment group continued VNS therapy and 95 patients in the sham group (delayed treatment) began stimulation. Delayed treatment patients followed the same study schedule that the treatment group followed during the acute study, including a 2-week stimulation adjustment period and 8-weeks of fixed stimulation. Patients were assessed on a monthly basis and served as their own controls for evaluation of efficacy, depression symptomology, and quality of life at 12 months.

Results: 180 patients with treatment-resistant depression who had completed at least 12 months of VNS therapy were included in the analysis. To compensate for placebo responders in the acute study, delayed treatment patients must have had a HRSD24 score >18 at the end of the 10-week acute sham treatment to be included in the 12-month analysis. Average age was 46.3 years, 64% were female. Mean length of illness was 25.5 years and average number of failed adequate trials in the current MDE was 3.5. One-year response rates, defined as a >50% improvement in depression symptoms as measured by the IDS-SR and HRSD24 (24 item clinician rated Hamilton Rating Scale for Depression) were 21% and 30%. One-year complete responders, defined as an IDS-SR >14 and HRSD24 >9, were 16% and 17%, respectively. Additionally, patients were assessed over time (months 9, 10, 11, and 12) to evaluate the durability of response. Sustained response was defined as >50% response at 1 of these visits and >40% response at 2 additional visits. At 1-year, 26% of patients were considered sustained responders.

Conclusion: This open, naturalistic study results are consistent with growing benefits of VNS therapy over time.

Source(s) of Funding: Cyberonics Inc.

POSTER NO. 195

COMPLETE REMISSION OF INDIVIDUAL SYMPTOMS AMONG DEPRESSED PATIENTS WITH SEVERE SYMPTOMS AT BASELINE

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Objective/Background: This analysis was conducted to compare the rates of complete remission of individual symptoms of depression among patients with high baseline levels of each symptom treated with venlafaxine, selective serotonin reuptake inhibitors (SSRIs), or placebo.

Methods: Original patient data from 31 randomized, double-blind studies were pooled to evaluate remission rates in 7422 depressed patients treated with venlafaxine/venlafaxine extended release (XR) (n=3273), SSRIs (n=3217), or placebo (n=932) for up to 8 weeks. The population of patients with more severe levels of each item of the $HAM\text{-}D_{21}$ at baseline was identified, and the percentages of patients experiencing complete symptom relief (HAM-D item score=0) on individual items were compared. The last-observation-carried-forward method was used to handle missing data.

Results: A significant advantage for venlafaxine over SSRIs and placebo was observed for the following items: depressed mood (32%, 28%, and 19% for venlafaxine, SSRIs, and placebo, respectively; both $P \leq 0.001$), anxiety-psychic (24%, 18%, 11%; both $P \leq 0.001$), somatic general (37%, 31%, 24%; both $P \leq 0.001$), genital (27%, 23%, 21%; P=0.007 vs SSRI, P=0.012 vs placebo), hypochondriasis (47%, 43%, 40%; P=0.038 vs SSRI, P=0.029 vs placebo), weight loss (82%, 75%, 73%; P=0.018 vs SSRI, P=0.044 vs placebo), feelings of guilt (48%, 41%, 28%; both $P \leq 0.001$), suicidal ideation (66%, 61%, 45%; P=0.020 vs SSRI, $P \leq 0.001$ vs placebo), insomnia-early (50%, 47%, 41%; P=0.046 vs SSRI, $P \leq 0.001$ vs placebo), insomnia-middle (48%, 44%, 42%; P=0.011 vs SSRI; P=0.009 vs placebo), and work and activities (28%, 24%, 18%; both $P \leq 0.001$).

Venlafaxine was associated with significantly greater rates of complete symptomatic relief compared with placebo only for diurnal variation (53% vs 40%, $P \leq 0.001$), depersonalization (57% vs 21%, P=0.019), insomnia-late (54% vs 42%, $P \leq 0.001$), and retardation (46% vs 33%, $P \leq 0.001$); and to SSRIs only for somatic-gastrointestinal (52% vs 45%, P=0.027).

SSRI vs placebo comparisons were significant for depressed mood ($P \leq 0.001$), anxiety-psychic (P=0.004), somatic general ($P \leq 0.001$), work and activities ($P \leq 0.001$), feelings of guilt ($P \leq 0.001$), suicidal ideation ($P \leq 0.001$), insomnia-early (P=0.006), insomnia-late (52% vs 42%, $P \leq 0.001$), diurnal variation (50% vs 40%, P=0.002), and retardation (45% vs 33%, $P \leq 0.001$).

Conclusion: Treatment with venlafaxine/venlafaxine XR is associated with significantly greater rates of complete relief of a wide variety of individual symptoms of depression relative to SSRI and placebo treatment among patients with severe symptoms at baseline. These results were similar to those observed in the overall population of patients (ie, regardless of baseline severity).

Source(s) of Funding: Wyeth Research

POSTER NO. 196

TOLERABILITY OF CONTROLLED RELEASE PAROXETINE IN PATIENTS PREVIOUSLY INTOLERANT TO SSRI/SNRI THERAPY

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Objective/Background: To evaluate the tolerability of controlled-release (CR) paroxetine in patients who stopped treatment with another SSRI or SNRI due to intolerance.

Methods: This study enrolled outpatients diagnosed with Major Depressive Disorder who had discontinued antidepressant treatment due to an adverse event from a recent (within 2 months) SSRI or SNRI regimen. Following discontinuation, patients were offered open-label paroxetine CR (flexible-dose, 12.5 to 62.5mg/day). The primary outcome measure in this 6-week study were the proportion of patients withdrawing during this paroxetine CR administration due to a treatment emergent adverse event (AE). Secondary outcome measures were recurrence rates on paroxetine CR of the AEs that produced intolerance to previous antidepressant treatment, overall AE incidence rates, and efficacy.

Results: The intent-to-treat population consisted of 646 patients. In total, 5.4% (35/646; 95% CI [3.6, 7.2]) of patients withdrew from the study due to a treatment emergent AE, 0.6% (4/646) withdrew due to lack of efficacy and 86.2% (557/646) completed the 6-week study. Twelve (1.9%; 95% CI [0.7, 3.0]) patients reported recurrence of the AEs that also caused intolerance to their prior antidepressant therapy. Nausea or vomiting were reported by 15.3% (99/646) of patients as a cause for withdrawal from prior antidepressants, while in only 3% (3/99) of these patients did a recurrence of nausea cause withdrawal from paroxetine CR. Similarly 13.5% (29/214) of male patients reported sexual side effects during prior treatment and only one (0.2%) of these patients withdrew due to a sexual side effect while taking paroxetine CR. For patients completing the trial, 74.7% (413/553), 95% CI [70.97, 78.40] of patients were considered CGI responders (very much improved, much improved).

Conclusion: Controlled-release paroxetine provides a useful treatment option providing antidepressant therapy to patients who previously have been intolerant to SNRI or immediate-release SSRI medication.

Source(s) of Funding: Funding was provided by GlaxoSmithKline.

POSTER NO. 197

DEPRESSION REMISSION RATES AMONG PATIENTS TREATED WITH VENLAFAXINE XR OR SSRIS USING TREATMENT ALGORITHMS

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Objective/Background: This study was designed to compare remission rates among patients with major depressive disorder (MDD) treated with venlafaxine extended release (XR) or selective serotonin reuptake inhibitors (SSRIs) using treatment algorithms and length of treatment guidelines.

Methods: In this open-label, rater-blinded, multicenter study, outpatients with MDD and HAM-D_{17} total score of at least 20 were randomly assigned to receive treatment with flexible doses of venlafaxine XR (75-225 mg/day; n=688) or an SSRI selected by the investigator (n=697 [fluoxetine (20-80 mg/day; n=114), paroxetine (20-50 mg/day; n=131), citalopram (20-40 mg/day; n=159), or sertraline (50-200 mg/day; n=193)]) for up to 180 days. Treatment was initiated at the lowest effective dose, with dose increases permitted at days 30 and 60 based on treatment response and dosing guidelines (maximum allowable doses were the upper limit of the FDA-approved dose ranges for depression). Remission was defined as a HAM-D_{17} total score <8.

Results: Mean maximum prescribed doses were venlafaxine XR 157 mg/day, fluoxetine 55 mg/day, paroxetine 41 mg/day, citalopram 35 mg/day, and sertraline 135 mg/day. Remission rates (ITT population; LOCF) were significantly greater in the venlafaxine XR group versus the SSRI group at days 30 (13% vs 9%), 60 (23% vs 18%), 90 (29% vs 24%), and 135 (33% vs 27%) ($P<0.05$ for all comparisons). Day 180 remission rates were 35.5% and 32% for venlafaxine XR and SSRIs, respectively (P=NS). Individual SSRI remission rates at day 180 were fluoxetine 36%, paroxetine 28%, citalopram 31%, and sertraline 33%.

Conclusion: These results suggest that venlafaxine XR is an effective treatment for MDD, and may bring patients to remission earlier in treatment compared with SSRIs when treatment algorithms and guidelines for duration of therapy are used.

Source(s) of Funding: Wyeth Research

POSTER NO. 198

IMPACT OF ESCITALOPRAM VERSUS NORETHINDRONE ACETATE AND ETHINYL ESTRADIOL ON DEPRESSION, VASOMOTOR SYMPTOMS, AND QUALITY OF LIFE IN PERI AND POSTMENOPAUSAL WOMEN: A RANDOMIZED TRIAL

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Background: The menopausal period has been associated with an increased medical and psychiatric morbidity, leading to a significant adverse impact on quality of life and social functioning. The use of hormone therapy (HT) for menopause-related mood symptoms has shown mixed results. In addition, its long term safety has been questioned. Novel strategies are needed for the treatment of menopause-related symptoms. This current study was designed to examine the efficacy of escitalopram compared to hormone therapy for the treatment of peri and postmenopausal women with depression and menopause-related symptoms.

Methods: Thirty-three peri and postmenopausal women, 40-60 years old, with depressive disorders (M.I.N.I. interview) and menopausal symptoms (Greene Climacteric Scale scores, GCS) were randomly assigned to receive an 8-week open treatment with escitalopram (flexible dose, 10-20 mg/day) or HT (ethinyl estradiol, 5mcg/day; norethindrone acetate, 1mg/day). Outcome measures include remission of depression (MADRS scores <10), and remission of menopause-related symptoms (50% decrease in GCS total scores from baseline, vasomotor sub-scores <3) at week 8. Quality of life was assessed by the MENQOL questionnaire. Subjects who did not achieve remission of depression and/or remission of menopause-related symptoms at week 8 entered in an 8-week adjunctive treatment phase, with a combination of escitalopram and HT.

Results: Thirty women (15 on escitalopram, 15 on HT) were included in the analyses (LOCF). Subjects randomly assigned to receive escitalopram or HT did not differ with respect to age, race, menopausal status, severity of depression, or severity of menopause-related symptoms at baseline ($p>0.05$, Mann-Whitney tests). After 8 weeks of treatment, 12 of 15 (80%) subjects treated with escitalopram achieved remission of depression, compared to 5 of 15 (33.3%) on hormone therapy ($p<0.05$, Fisher's Exact test). Both treatments promoted alleviation of vasomotor symptoms (40% versus 46.6%, respectively; $p=0.74$, Pearson chi-square test). At week 8, remission of depression AND remission of menopause-related symptoms was achieved by 60% of women on escitalopram, compared to 13.3% on HT ($p<0.05$, Pearson Chi-square). Both treatments improved quality of life (MENQOL scores) significantly. During the adjunctive treatment phase, escitalopram was more efficacious than HT in promoting further clinical improvement and QOL.

Conclusions: Escitalopram is an efficacious treatment for symptomatic menopausal women, not only for depression but also for other menopause-related symptoms and quality of life improvement. The use of escitalopram may constitute an interesting treatment option for women who are unable or unwilling to receive treatment with HT.

Source(s) of Funding: Supported by a research grant from Forest Laboratories, Dr.Soares is a recipient of a 2003 NARSAD YI Award

POSTER NO. 199

ANTIDEPRESSANT USE IN VETERANS WITH HEPATITIS C

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Objective/Background: Approximately 6 to 7% of veterans are infected with hepatitis C virus (HCV), and depression is a common co-morbid diagnosis. If left untreated, depression can be a cause of interferon treatment non-compliance or failure. This study examines antidepressant treatment rates in veterans with HCV prior to interferon treatment.

Methods: 478 veterans (458 male, 20 female, 53.8 ± 6.4 yrs) gave informed consent to monitor their treatment, and 379 (363 male, 16 female) completed a Beck Depression Inventory-II (BDI-II) as part of their initial HCV specialty clinic appointment. Review of pharmacy records yielded information regarding active prescriptions for psychotropic medications.

Results: Of the 478 veterans enrolled in the study, 31.6% (151) were taking a psychotropic medication (prescribed for depression, anxiety, sleep difficulty, pain, psychotic symptoms, etc.). 27.6% (132) were taking an antidepressant, most frequently, an SSRI. Analgesics were the next most commonly prescribed drug, with 20.1% (96) taking an opioid and 6.7% (32) taking other analgesics.

Approximately one-third (129/379 or 34%) of veterans who completed the BDI-II scored 20 or higher, indicating a moderate to severe level of depression. Of note, of the 129 moderately or severely depressed patients, 72 (56%) were not taking an antidepressant. The 260 veterans not prescribed antidepressants upon enrollment had a significantly lower mean BDI-II score compared with the 119 veterans taking an antidepressant (14.2 vs. 19.1, $p<.0001$).

Conclusion: Depression is common among veterans with HCV, and in this sample, one-third had moderate to severe depression. Although antidepressants were the most commonly prescribed psychotropic medication, over half (56%) of moderately to severely depressed patients were not currently prescribed an antidepressant. Our study suggests that routine screening for psychiatric illness in HCV patients is warranted and will facilitate identification and treatment of depression.

Source(s) of Funding: Veteran's Administration Merit Review Grant VA Hepatitis C Resource Centers

POSTER NO. 200

MULTI-SITE STUDY OF OUTPATIENT MULTIPLE MEDICATION USE IN RELATION TO AGE AND ANTIDEPRESSANT DRUG USE

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Objective/Background: Learn that patients on antidepressants(ADs) are at greater risk for multiple medication use than age matched patients not on antidepressants and how that knowledge can aid in focusing efforts to identify and avoid potential adverse drug-drug interactions.

Methods: Two stratified random samples from prescription databases of 7 VA sites: 1991 patients deemed to have a current antidepressant supply, including 891 patients < 60 years of age and 1100 ≥ 60 years of age and a subset of 3732 patients with no antidepressant prescriptions during the prior 365 days, including 1195 patients <60 years of age and 2535 patients ≥ 60 years of age. Outcome measures: mean (S.D.) and median number of SG drugs in each subset; frequently used VA drugs/classes; multiple medication use (0, 1, 2-4, 5-7, or 8+ SG drugs)

Results: Patients on an AD versus those not on an AD had higher multiple medication use and more complex drug regimens. Ordinal multivariate analysis of multiple medication use revealed odds ratios of 3.32 for antidepressant use, 2.85 for other psychotropic drug use, and 2.57 for age (all, $p<0.0001$).

Conclusion: AD use marks a population at substantial risk for drug-drug interactions, independent of age.

Source(s) of Funding: VISN 15 of Veterans Administration and an unrestricted educational grant from Pfizer.

POSTER NO. 201

COMPARATIVE EFFICACY OF SERTRALINE VERSUS VENLAFAXINE-XR IN SEVERE DEPRESSION

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Objective: To compare antidepressant efficacy of sertraline versus venlafaxine-XR in a subgroup of depressed patients with severe depression.

Methods: An international, 8-week, double-blind study of 163 outpatients with Major Depressive Disorder (MDD) who were randomized to sertraline (50-150 mg/day; n=79) and venlafaxine-XR (75-225 mg/day; n=84) followed by a 2-week taper. A severe depression subgroup was defined by baseline HAM-D total score $\geq$26 or CGI-S$\geq$5. Response was defined as $\geq$50% reduction in HAM-D; remission was defined as HAM-D$\leq$7. Intent-to-treat (ITT) analyses were undertaken at week 8 with the last observation carried forward (LOCF). These analyses were repeated at week 8 amongst completers. Changes from baseline in HAM-D and Q-LES-Q scores were analysed using analysis of covariance; least-square (LS) means and p-values are presented. The Cochran-Mantel-Haenszel test was used to produce p-values for differences in response and remission rates between groups.

Results: Eighty-four (52%) of 163 outpatients met criteria for severe MDD (74% female; mean age, 36 years; mean baseline HAM-D, 26). Seventy percent of the 84 patients had a HAM D (n=59) assessment available at week 8 and were included in the week-8 completer analyses. In this severe MDD subgroup, LS mean change from baseline on HAM-D total score was similar for sertraline and venlafaxine-XR; week-8/LOCF (-17.8$\pm$1.7 vs. -15.4$\pm$1.6; p=0.24), week-8 completers (-20.1$\pm$1.5 vs. -17.9$\pm$1.5; p=0.25). Sertraline and venlafaxine-XR resulted in similar HAM D response rates (week-8/LOCF, 71% vs. 71% [p=0.82]; week-8 completers, 79% vs. 90% [p=0.57]), as well as similar HAM-D remission rates (week-8/LOCF, 63% versus 52% [p=0.27]; week-8 completers, 76% versus 63% [p=0.18]).

Conclusion: Sertraline and venlafaxine-XR were found to have similar antidepressant efficacy in severe MDD.

Source of Funding: Pfizer Pty Limited.

POSTER NO. 202

THE POTENTIAL FOR CLINICALLY SIGNIFICANT DRUG-DRUG INTERACTIONS IN PATIENTS RECEIVING CYP 2D6 MODEL SUBSTRATE/DRUGS AND FLUOXETINE/PAROXETINE OR SERTRALINE

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Background/Objective: Learn about the frequency of potentially clinically significant cytochrome P450 mediated drug-drug interactions in VA patients on fluoxetine or paroxetine.

Methods: Determined the frequency of the combined use of fluoxetine/paroxetine versus sertraline with drugs principally cleared via 2D6 in VA outpatients (461 on fluoxetine/paroxetine and 435 on sertraline). Determined whether the therapeutic index and dose of the co-administered 2D6 substrate/drug posed a risk for a potentially dangerous drug-drug interaction (DDI), given substantial inhibition of 2D6.

Results: 39.7% of patients being treated with fluoxetine/paroxetine were also receiving a 2D6 model substrate/drug versus 34.2% of patients on sertraline with 1 out of 4 in both groups being on a 2D6-model substrate/drug with a narrow therapeutic index. 21.3% of the fluoxetine/paroxetine patients were receiving a dose of the 2D6 model substrate/drug high enough to cause a significant risk for a serious DDI. In 50% of the drug combinations, the DDI was not identified by the drug information system employed.

Conclusions: One out of 12 VA outpatients on fluoxetine/paroxetine were at risk for a clinically meaningful 2D6 mediated DDI.

Source of Funding: VISN 15 of the Veterans Administration and an unrestricted educational grant from Pfizer

POSTER NO. 203

ESCITALOPRAM IMPROVES SOMATIC SYMPTOMS OF DEPRESSION

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Objective/Background: Somatic symptoms are commonly associated with depression. Escitalopram has been shown to improve a wide spectrum of symptoms associated with depression and anxiety disorders. We hypothesized that escitalopram would similarly improve somatic symptoms in depressed patients.

Methods: Two 8-week, randomized, placebo-controlled trials of escitalopram 10-20mg/day that utilized the Hamilton Depression Rating Scale (HAMD) have been performed in patients with moderate-to-severe depression (mean baseline HAMD=25). The design of these trials were similar, and data from these trials were pooled. Somatic symptoms were measured by the HAMD Item 13 (Somatic Symptoms - General). LOCF results are presented.

Results: Escitalopram treatment (N=365) led to significantly greater improvement in HAMD Item 13 scores than placebo treatment (N=244; -0.635 vs. -0.495; $p<0.05$). In the overall patient population, the mean change in HAMD total score from baseline to week 8 was statistically significant for escitalopram versus placebo, consistent with previously published results. In patients with clear-cut somatic complaints, defined as HAMD Item 13 score of 2 (N=393), mean change from baseline in HAMD total score from baseline to week 8 was significantly greater for escitalopram than placebo (-11.397 vs. -9.010; $p<0.05$).

Conclusion: Escitalopram significantly improves somatic symptoms of depression, and is an effective antidepressant in depressed patients with somatic complaints.

Source(s) of Funding: Forest Labs

POSTER NO. 204

CHANGES IN BRAIN FUNCTION DURING PLACEBO LEAD-IN AND TREATMENT OUTCOME IN CLINICAL TRIALS FOR MAJOR DEPRESSION

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Objective/Background: Changes in symptoms have been noted during single-blind placebo lead-in, however no study has examined changes in brain function during placebo lead-in among depressed subjects. The relationship between neurophysiological changes during placebo lead-in and eventual medication treatment outcome is unknown.

Methods: Data were pooled from 51 depressed subjects who participated in one of two independent double-blind placebo-controlled trials; the trials utilized fluoxetine, 20 mg, (n=24) and venlafaxine, 150 mg (n=27), respectively, as the active medication. A one-week single-blind placebo lead-in preceded eight-weeks randomized treatment with medication or placebo. Brain function was monitored at baseline and end of placebo lead-in using quantitative electroencephalograghy (QEEG) cordance and clinical response was measured as the final Ham-D score at the end of eight weeks. We assessed the relationship between change in prefrontal cordance at end of placebo lead-in and final Ham-D score for the total sample, and separately for subjects randomized to medication or placebo. We also examined subject demographics, treatment history, and neurocognitive function as potential covariates of change in prefrontal cordance at end of placebo lead-in.

Results: Change in prefrontal cordance during placebo lead-in was associated with clinical response across treatment conditions ($r = .33$, $p = .02$), and separately for subjects randomized to medication ($r = .43$, $p = .03$) but not placebo. Decreases in cordance during placebo lead-in were associated with lower final Ham-D scores. In the aggregate sample, change in prefrontal cordance at end of lead-in was found to co-vary with gender ($r = .35$, $p = .01$) and antidepressant treatment history ($r = .30$, $p = .04$) where males and subjects without any prior history of antidepressant treatment were more likely to show decreases in prefrontal cordance during placebo lead-in. Multiple linear regression analysis indicated that gender and treatment history explained a small but significant amount of the variance in change in prefrontal cordance during placebo lead-in ($R2 = .18$, $p = .01$).

Conclusion: Change in prefrontal brain function during placebo lead-in appears to provide a pretreatment biomarker of antidepressant treatment outcome in clinical trials for major depression. A portion of the variance in prefrontal neurophysiological change during placebo lead-in can be explained by gender and antidepressant treatment history.

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POSTER NO. 205

COMPARING METHODOLOGIES FOR ASSESSING ONSET OF ACTION IN NEUROPSYCHIATRIC CLINICAL TRIALS

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Objective/Background: A major disadvantage of antidepressant medications is their delay in onset of effect. Given the importance of onset of action, this is an active area of investigation.

Methods: The present investigation compared the Type I error rates and power of survival analyses (KM=Kaplan-Meier, PH= Proportional Hazards Regression) and a categorical mixed-effects model repeated measures approach (MMRM-CAT) in simulated data. Four scenarios mimicking antidepressant clinical trials were created by varying mean improvements over time. Within each scenario, three sets of data were created by either leaving the data complete, or deleting observations to generate data missing not at random according to one of two dropout patterns. Either all 16 (twice weekly for 8 weeks) postbaseline visits were included (frequent visit assessment) in the analyses or only those observations corresponding to weeks 1, 2, 4, 6, and 8 (traditional visits). Onset was defined as a 20% improvement from baseline that was sustained at all subsequent assessment times. Both KM and categorical MMRM provided appropriate control of Type I error, while with PH the rate of false rejections was lower than expected. The categorical MMRM analysis generally provided greater power and was biased less by missing data than either KM or PH.

Results: A frequent visit schedule improved precision of KM and PH analyses compared with a traditional visit schedule. Whether or not this increased precision increased power depended on the mean trajectories over time. With the categorical MMRM approach, minimal precision was gained by using a frequent visit schedule. The categorical MMRM analysis using a traditional visit schedule yielded more power than KM and PH with a frequent visit schedule.

Conclusion: These results suggest that while a variety of analyses are needed to fully characterize onset of action, the categorical MMRM approach is one of the useful methods and may allow accurate assessments of onset from traditional designs.

Source(s) of Funding: Eli Lilly and Company

POSTER NO. 206

COMPARATIVE PREVALENCE OF PSYCHOTROPIC MEDICATION FOR YOUTH: MEDICAID VS. PRIVATE INSURANCE

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Objective/Background: The psychotropic medication prevalence for Medicaid-insured youth is consistently higher than that of privately insured youth. Disaggregating the Medicaid population into major eligibility categories permits identification of a socioeconomic group similar to the privately insured. The state children's health insurance program (SCHIP) category is socio-economically similar but has differences in race/ethnicity, age distribution and parent-reported health impairment that has been shown to influence psychotropic medication prevalence. Objective. To determine if psychotropic medication prevalence of youths enrolled in SCHIP and privately insurance programs differ.

Methods: Prescription claims and enrollment data for SCHIP enrollees from a mid-Atlantic Medicaid state were analyzed in a cross-sectional analysis for 2 one-year periods (1999 and 2000) and for continuously enrolled youths for the year 2000. Age-specific prevalence for selective serotonin reuptake inhibitors (SSRIs), stimulants and 'any psychotropic' medication was calculated. Prevalence was defined as 1 or more prescriptions per 100 enrollees. Comparable measures of psychotropic medication prevalence were extracted from published studies of multi-state datasets of privately insured youths from MarketScan, Express Scripts and United Health Group affiliated health plans.

Results: Youths enrolled in SCHIP had significantly higher psychotropic medication prevalence rates than privately insured youths in all 8 comparisons regardless of the medication group measured. The difference in rates ranged from a low of 19% for SSRIs to a high of 60% for stimulants and 'any psychotropic'. Based on previous studies, the predominance of minority youths (62%) and youths less than 5 years (53%) in the SCHIP population should have lowered the psychotropic prevalence, while SCHIP parent-reported health impairment would be expected to increase the rate. The surveyed state Medicaid program did not require a co-payment or have a restrictive formulary, thus serving to increase Medicaid medication prevalence relative to private insurance.

Conclusion: Conclusion. Unexpectedly, SCHIP psychotropic medication prevalence from this representative state Medicaid population was substantially higher than prevalence rates for privately insured youths. Additional research within the same geographic region is needed so that the influence of insurance plan differences in co-payments and formulary restrictions can be systematically assessed.

Source(s) of Funding: Source of Funding. U of Maryland DRIF funds

POSTER NO. 207

ADJUNCT MODAFINIL REDUCES ANTIDEPRESSANT-INDUCED SEDATION IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Objective/Background: Symptoms such as fatigue and excessive sleepiness may not fully resolve in patients with major depressive disorder treated with antidepressants (AD), and may be side effects associated with these therapies. Sedating side effects of AD therapy may contribute to noncompliance and discontinuation of treatment. Adjunct modafinil has been shown to reduce fatigue and improve wakefulness in patients with major depressive disorder. We evaluated adjunct modafinil in patients with major depressive disorder experiencing sedating side effects of AD.

Methods: 17 patients with depressive disorder (1 patient had depression and generalized anxiety disorder, and 2 patients had depression and posttraumatic stress disorder [DSM-IV]) entered a 3-week open-label study. Patients were taking selective serotonin reuptake inhibitors (SSRIs) or Effexor (venlafaxine HCl), and reporting sedating side effects. All patients received modafinil 50-400 mg/day with flexible weekly titration, in addition to existing AD. Assessments included the Epworth Sleepiness Scale (ESS), Fatigue Severity Scale (FSS), Hamilton Rating Scale for Depression (HAM-D), and Short-Form Health Survey version 2 (SF-12v2). Side effects were measured using the Udvalg for Kliniske Undersogelser (UKU) rating scale.

Results: Adjunct modafinil significantly improved wakefulness at all time points measured (ESS; $p<0.01$ vs baseline) and decreased fatigue from week 2 onwards (FSS; $p<0.01$). Adjunct modafinil significantly improved mood at all time points (HAM-D total score; $p<0.001$). Treatment was associated with significant improvements in health-related quality of life by week 2 (SF-12v2 total score; $p<0.05$). In particular, improvement in health-related quality of life was seen for the emotional health domain score at weeks 1, 3, and last visit, and for the physical health domain score at last visit (SF-12v2 domain scores; $p<0.05$). Modafinil was well tolerated. Most common adverse events were headache, stomachache, and jitteriness.

Conclusion: In patients with sedating side effects of AD, adjunct modafinil may be efficacious in improving wakefulness, fatigue, mood, and health-related quality of life.

Source(s) of Funding: Cephalon, Inc., West Chester, PA

POSTER NO. 208

FLEXIBLE DOSE ARIPIPRAZOLE IN PSYCHOSIS OF ALZHEIMER'S DEMENTIA (AD)

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Objective: To evaluate flexible-dose aripiprazole for treatment of institutionalized patients with psychosis of AD.

Methods: 256 institutionalized patients with psychosis of AD were randomized to placebo or flexible dose of aripiprazole (starting dose, 2mg/d) for 10 weeks. Efficacy assessments included the NPI-NH, BPRS, CGI, CMAI, and Cornell Scale for Depression in Dementia.

Results: The mean aripiprazole dose used during the study was 8.6 mg/day (range, 2 15 mg/day). Comparable improvements in NPI-NH Psychosis subscores were observed at week 10 in aripiprazole and placebo groups. Aripiprazole-treated patients showed significant improvement compared with placebo in NPI-NH Total scores (-16.4 vs -10.0, p=0.009) and BPRS (-7.7 vs -5.1, p=0.031). Significant improvements in agitation and mood symptoms were observed using CMAI and Cornell Depression Scales and CGI-I scores. Discontinuation rates due to AEs were similar in the two groups (aripiprazole, 13%; placebo, 8%). EPS-related AEs were comparable in the two treatment groups (5% with aripiprazole and 4% with placebo).

Conclusion: Aripiprazole treatment resulted in significant improvement over placebo in NPI-NH and BPRS total scores in institutionalized patients with psychosis of AD. The improvement was most pronounced for agitation, behavioral, and mood symptoms. Aripiprazole treatment was well tolerated in this elderly population.

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POSTER NO. 209

ANTIDEPRESSANT TRENDS AMONG CHILDREN AND ADOLESCENTS DIAGNOSED WITH DEPRESSION: 1990-2001

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Objective: Since 1998, the use of selective serotonin reuptake inhibitors (SSRIs) has been advocated as first-line treatment for depression in children and adolescents. This study was designed to discern trends in the prevalence of office-based visits resulting in a diagnosis of depression among children and adolescents age 5-18 years, and trends in the prescribing of antidepressants for its treatment.

Methods: Using data from the National Ambulatory Medical Care Survey, the number and rate of office-based physician visits resulting in a diagnosis of depression (ICD-9-CM codes 296.2 - 296.36; 300.4; or 311), and the prescribing of antidepressants (by type) were discerned for the years 1990-2001. Trend analysis was conducted using three, 4-year time intervals: 1990-93; 1994-97; 1998-01.

Results: Over the time-frame examined, the U.S. population-adjusted rate of office visits documenting a diagnosis of depression increased 2.4-fold, from 12.9 per 1,000 children and adolescents, to 31.1 per 1,000. The percent of patients prescribed an antidepressant increased from 44.4% to 59.3%; receipt of an SSRI increased from 20.7% to 39.7%; and receipt of a tricyclic antidepressant declined from 21% to 2.7%.

Conclusion: These data reveal significant growth in the rate of children and adolescents diagnosed with depression in the U.S., and significant growth in the prescribing of antidepressants for its treatment.

Source of Funding: 2001 Independent Investigator Award, National Alliance for Research on Schizophrenia and Depression.

POSTER NO. 210

ESCITALOPRAM IN THE TREATMENT OF COMPULSIVE BUYING DISORDER AND KLEPTOMANIA

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Background: Compulsive Buying Disorder (CBD) may affect 2% to 8% of the adult U.S. population (Faber and O'Guinn 1992). Kleptomania is estimated to affect 6 per 1000 U.S. adults (Goldman 1998). Both are associated with considerable personal and familial suffering (Koran 1999, 2002). Our double-blind (Koran 2003) study suggested that CBD responds well to citalopram. Successful SSRI treatment of kleptomania cases has been reported (Koran 1999). As a result, we are conducting controlled trials of escitalopram for these two disorders.

Methods: We are enrolling CBD adults meeting criteria suggested by McElroy et al. (1994) for 1 year and compulsively buying at least weekly for the past three months. Kleptomania subjects are adults with kleptomania of " 1 year's duration, meeting DSM-IV criteria and marked by court referral or stealing " once weekly. We exclude individuals with psychotic disorders, alcohol or substance abuse, bipolar disorder or OCD. Subjects receive open-label escitalopram 10 mg/day for 4 weeks and if not "responders," take 20 mg/day for 3 additional weeks. A CBD "responder" has a " 50% decrease in Y-BOCS-Shopping Version (Y-BOCS-SV) scale score and a CGI-I score of much or very much improved. A kleptomania "responder" decreases weekly theft frequency by " 50% and has a CGI-I score of much or very much improved. Responders at week 7 are randomized to continue for 9 weeks (buying) or 16 weeks (kleptomania) on double-blind escitalopram or placebo.

Results: We have enrolled 11 CBD patients and 13 kleptomania patients, of 24 planned for each study. Ten CBD completed the seven weeks of open-label escitalopram; one discontinued by leaving the area. Mean credit card debt at baseline was $11,870 (range $0-$35,800); two had declared bankruptcy. Six subjects (55%) were responders. The 10 completers' mean Y-BOCS-SV score decreased from 25.6 (SD 3.7) at baseline to 13.1 (SD 12.3) at end of week 7. Of the six responders, three relapsed during the double-blind, placebo-controlled, escitalopram discontinuation phase, but the blind remains unbroken. Eleven kleptomania patients completed the seven weeks of open-label escitalopram; two discontinued for drowsiness. Eight subjects (62%) were responders. Of these eight, four relapsed during the double-blind, placebo-controlled phase, but the blind remains unbroken.

Conclusions: Early results suggest that escitalopram is well tolerated and has a therapeutic effect in treating compulsive buying and kleptomania. Firm conclusions must await study completion and breaking the blind.

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POSTER NO. 211

ESTABLISHING TECHNOLOGY-BASED COMMUNICATIONS IN THE SEQUENCED TREATMENT ALTERNATIVES TO RELIEVE DEPRESSION (STAR*D) PROJECT

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While efficient communication is essential in conducting large multi-center clinical trials, very little information is available on the actual methods that can be implemented to improve communication. An integrated technology-based communications system was developed for the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project, a multi-center series of clinical trials designed to prospectively evaluate which of several treatments are most effective for participants who report an unsatisfactory clinical outcome to an initial and, if necessary, subsequent treatment for depression.

The STAR*D communication system includes a multi-faceted study web site, automated reporting via e-mail, and an online data correction mechanism, all implemented to enhance traditional methods of communication. The STAR*D web site (www.star-d.org) has a password-protected area reserved for study researchers which includes a project directory, discussion boards, document sharing, and a help desk. The help desk is used to address issues that arise during the course of the study, ranging from clinical management to data collection procedures. Questions are automatically directed to appropriate personnel, and responses are disseminated promptly via e-mail, and also stored in a database for future reference.

Automated reporting via e-mail is based on an integrated set of programs that selects information, creates reports, determines who should receive a copy of the reports, and sends the reports via e-mail. The reports are distributed at different frequencies depending on the type of report, and e-mail addresses are taken from the dynamic web site directory to ensure up-to-date addresses.

To correct data inconsistencies, a program creates a unique query report for each site's coordinator, identifying problem forms and specifying the inconsistencies. An automated process saves the report and attaches it to an e-mail that is automatically directed to the appropriate site coordinator. The e-mail message contains links to a server for each query. When selected, these links will open an online version of the original data entry form as it exists in the database, with the problematic fields outlined in red. The site's coordinator compares the data from the query report to the data from the patient's files and makes the necessary changes by typing directly on the online form, then clicks a SUBMIT button when complete.

This system fills the gaps in traditional communications methods, reduces the burden on the research team, and improves the quality of the data produced by the study in a cost-efficient manner.

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POSTER NO. 212

A PRE AND POST ANALYSIS OF CLOZAPINE BLOOD LEVELS AND CLINICAL GLOBAL IMPRESSIONS FOR SUBJECTS SWITCHED FROM NOVARTIS BRAND CLOZARIL TO IVAX BRAND CLOZAPINE

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Objective/Background: Clozapine, an atypical antipsychotic, maintains unsurpassed efficacy in the treatment of chronic and severe psychotic disorders. Additionally, clozapine is the only atypical antipsychotic with available generic equivalents. Economic advantages of using generic equivalents are only assured if the clinical outcome is comparable between products. This study compares 103 subjects before and after switching from Novartis brand Clozaril to Ivax brand clozapine. Clozapine blood levels and clinical global inventories were captured before and after 103 subjects were switched.

Methods: 103 subjects residing in the same long-term care facility for the mentally ill were changed from Novartis brand Clozaril to Ivax brand clozapine. Prior to the switch, subjects were assessed for clozapine blood levels and were administered the Clinical Global Impression (CGI)-Severity scale. Two weeks after the switch subjects were again assessed for clozapine blood levels and CGI-Improvement scales were administered. Blood draws occurred between 6 and 10 am. The measures were administered as part of routine patient care and collected retrospectively.

Results: The sample of 103 subjects consisted of 76 males and 27 females, with a mean age of 44.9 years. The daily mean dose pre-switch was 342.5mg (SD=261) and post-switch was 362.4mg (SD=247). The mean blood levels differed 5.8%. The difference between means of the two products was not clinically significant ($p>0.10$). Eight (7.8%) subjects required dose adjustments after the switch, with 6 increased and 2 decreased. Clozapine blood levels increased for 5 of the 6 subjects with increased clozapine doses, and 1 of the 2 subjects had clozapine blood levels drop in line with their decreased dose. The number requiring dose adjustments was not clinically significant ($p>0.10$). The CGI-Severity score averaged 4.4 (SD=1.2), indicating that subjects fell between Moderately and Markedly Ill at baseline. The CGI-Improvement scale averaged 3.9 (SD=0.5), indicating No Change from baseline.

Conclusion: Novartis brand Clozaril and Ivax brand clozapine were statistically equivalent for clozapine blood levels. The CGI scores indicate that the significantly mentally ill subjects faired comparatively on both brands, as assessed by clinical judgment. Overall, results suggest that the two products are equivalent and the switch has been deemed successful. A double-blinded, prospective, rigorously controlled, crossover design using an expanded subject pool would provide more conclusive results.

Sources of Funding: This research was supported by a grant from Ivax Pharmaceuticals.

POSTER NO. 213

IMPLEMENTATION OF A COMPUTERIZED TREATMENT ALGORITHM FOR DEPRESSION IN REAL WORLD PRACTICE

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Objective/Background: The purpose of this study is to examine the feasibility of using a Computer Decision Support System (CDSS) for the treatment of psychiatric disorders during outpatient treatment visits. The study also identifies ways to overcome barriers to the implementation of Information Technology (IT) systems in clinical practice to enhance quality of care. Background: There is an increasing emphasis on the use of information systems to improve the quality of care in medicine. These systems range from simple electronic health records to more complex decision support systems that provide treatment recommendations and prompts for physicians to implement best practices in clinical care. Despite the proven efficacy of IT systems, physicians have been reluctant to integrate these resources in clinical practice. To successfully implement an IT system into the work environment barriers to change must be identified, and subsequently eliminated, reduced or managed. Behavior change and IT integration models suggest that in order for an IT system, such as the pharmacotherapy CDSS under study, to be accepted into clinical practice, it must be easy to use, helpful, quick, efficient, combined with effective training, and followed with adequate IT support.

Methods: As part of a program to evaluate the effects of implementation of a pharmocotherapy CDSS in the public mental health sector, five MHMR clinics in Texas were identified for the feasibility test. The participants were 15 physicians across the five sites, over a 12-month period. All patients had, clinician diagnosed, Major Depressive Disorder. The CDSS used, CompTMAP, is a computer decision support system for the medication management of patients with MDD. The system provides a range of medications options used for primary syndromes, strategies for augmenting or changing medications, dosing recommendations, as well as tracking over time, and integrating into recommendations, physician and patient ratings of symptom reduction and side effect burden.

Results: As additional components of the IT integration and behavior change models were incorporated into the CDSS implementation, physician utilization and compliance increased. Many of the barriers to change (ease of use, speed, helpfulness, and efficiency) were eliminated through continued modification of the CDSS program. Physicians testing the initial beta versions, the basis for modifications, were prone to having a negative perception of usefulness during periods of revision. Increased training time and IT support, also aided in the successful implementation.

Conclusion: It is feasible to implement a comprehensive computerized treatment algorithm, in the form of a pharmacotherapy CDSS, into a busy clinical practice.

Source(s) of Funding: Funded in part by NIMH 1-R01-MH064062-01A2 (MHT) and the Brown Foundation (MHT)

POSTER NO. 214

A COMPREHENSIVE RETROSPECTIVE STUDY OF ASSOCIATIONS BETWEEN DIABETES AND TREATMENT WITH RISPERIDONE, OLANZAPINE, QUETIAPINE, AND CONVENTIONAL ANTIPSYCHOTICS

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Objective/Background: Retrospective studies using large patient databases have had conflicting findings regarding diabetes risks associated with antipsychotics. Sensitivity of findings to study design was assessed.

Methods: Claims data for thousands of patients with psychoses both treated and untreated with antipsychotics were analyzed. Screening for preexisting diabetes, identification of diabetes with prescription claims only, and antipsychotic monotherapy provide better control for confounding influences and represent a stronger study design. Diabetes odds ratios for patients treated with risperidone, olanzapine, quetiapine, or conventional antipsychotics versus untreated patients were estimated varying the above criteria. These were performed for all patients and for patients stratified by low, medium, and high dose levels. Logistic regression controlled for patient age, sex, type of psychosis, length of observation/treatment, preexisting excess weight, and use of other drugs with potential diabetogenic effects.

Results: Under a weaker study design, patients taking all of the antipsychotics had significantly higher odds of diabetes relative to patients untreated with antipsychotics. Differences among the antipsychotics were relatively small; odds ratios with 12 months of treatment were: risperidone 1.388 (confidence interval [CI]: 1.276-1.509), olanzapine 1.331 (CI: 1.224-1.446), quetiapine 1.394 (CI: 1.247-1.559), and conventionals 1.365 (CI: 1.238-1.503). Under a stronger study design, relative odds for quetiapine became statistically insignificant and declined sharply, 1.087 (CI: 0.742-1.612), while those for olanzapine and conventional antipsychotics remained significant and increased, 1.858 (CI: 1.549-2.238) and 1.755 (CI: 1.381-2.221). The overall odds ratio for risperidone also declined and became nonsignificant, 1.224 (CI: 0.962-1.562). When stratified by dose, quetiapine alone showed a lack of statistical significance at all dose levels. For patients taking conventional antipsychotics, odds of diabetes were significantly higher at all dose levels than for untreated patients; for patients taking olanzapine, odds were higher at medium and high doses; and for patients taking risperidone, odds were higher at high dose only.

Conclusion: In large database studies, estimated risks of diabetes among antipsychotics are affected by study design. With a more reliable design, the estimated risks associated with quetiapine and risperidone are lower than those associated with olanzapine and conventional antipsychotics.

Source(s) of Funding: The research presented was supported by AstraZeneca Pharmaceuticals LP.

POSTER NO. 215

IMPROVEMENT IN QUALITY OF LIFE WITH RISPERIDONE AUGMENTATION IN TREATMENT-RESISTANT DEPRESSION

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Objective/Background: To evaluate the effect of adjunctive risperidone treatment on quality of life in patients with treatment-resistant depression (TRD).

Methods: Data from the open-label treatment phase (4-6 weeks) of an international study designed to evaluate the efficacy, safety, and maintenance effect of risperidone augmentation to SSRI-treatment in TRD. Quality of life was evaluated using the short form of Quality-of-Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Change in Q-LES-Q from baseline was analyzed by paired t test. Correlation analyses between MADRS and Q-LES-Q change scores were performed using Pearson method.

Results: This analysis included 386 subjects, mean age 47.1. Baseline and endpoint mean (SD) Q-LES-Q scores were 42.8 (14.6) and 56.0 (18.6), indicating an improvement of 13.2 with risperidone augmentation ($P<.0001$). Significant improvements were observed as early as day 7 ($P<.0001$). Q-LES-Q item 15, medication satisfaction, was rated as good or very good by 61% of subjects. Correlation between Q-LES-Q and MADRS total change scores at endpoint was -0.6.

Conclusion: These findings suggest that augmentation with risperidone rapidly and significantly improves quality of life in TRD patients. Consistent with previous work, the correlation between Q-LES-Q and MADRS indicates a meaningful relationship between quality of life improvement and symptom relief.

Source(s) of Funding: Source of funding: Janssen Pharmaceutica Products, L.P.

POSTER NO. 216

COURSE OF WEIGHT & METABOLIC BENEFITS 1 YEAR AFTER SWITCHING TO ZIPRASIDONE

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Objective: To determine the long-term course of short-term improvements in weight and metabolic side effects among schizophrenic outpatients recently switched to ziprasidone.

Methods: Three open-label, flexible-dose continuation studies enrolled stable completers of 6-week trials of outpatients who were switched from either conventionals (n=71), olanzapine (n=71), or risperidone (n=43) to ziprasidone. Follow-up to 1 year of ziprasidone monotherapy (median 30.5 weeks) permitted longitudinal assessment of improvement in weight and metabolic side-effect profile using ITT analysis.

Results: Patients switched to ziprasidone from risperidone or olanzapine exhibited continued weight loss and lowering of BMI over 1 year. For the pre-switch olanzapine group, additional weight loss was 5.7 lb ($P<0.0001$) over and above the initial 6-week weight loss of 3.7 lb. For the pre-switch risperidone group, the additional weight loss was 9.3 lb ($P<0.001$) over and above the initial 2.0-lb weight loss. Metabolic improvements in triglycerides and cholesterol noted at endpoint of the 6-week switch were sustained over 1 year. Reduction in median triglycerides was 31.0 mg/dL ($P=0.0001$) for the pre-switch olanzapine group, and 17.0 mg/dL ($P<0.05$) for the pre-switch risperidone group.

Conclusions: Schizophrenic outpatients switched from olanzapine or risperidone to ziprasidone continued osing weight for up to 1 year. Other initial 6-week improvements in metabolic parameters were sustained during long-term ziprasidone monotherapy.

Source of Funding: Supported by funding from Pfizer Inc.

POSTER NO. 217

THE GRID HAMD: AVAILABILITY OF A NEW STANDARDIZED METHOD FOR THE ASSESSMENT OF DEPRESSION

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Background: The Hamilton Depression Rating Scale is the most widely used rating scale for assessing depression severity in clinical trials. However, there are :

- Multiple versions of the scale
- Multiple conventions for administering the scale.
- Inconsistent use of a structured guide for the interview

This has resulted in unnecessary challenges to raters expected to apply multiple different rating conventions or different modes of administration simultaneously in different studies.

The Hamilton Depression Rating Scale has also been criticized for other reasons including:

- Lack of clarity of the item anchor descriptions
- No operationalization of the intensity and frequency domains needed to arrive at a severity rating

Method:

- The DRSST group was formed by representatives from academia, the government, and the pharmaceutical industry to examine how to improve the Hamilton Depression Rating Scale
- A Core Working Group was established to develop a consensus based instrument preserving the original items but improving its administration Draft document was sent to more than 200 worldwide experts in the treatment and assessment of depression and their input incorporated.
- Three Components Developed:

GRID scoring system:

- Incorporates scoring instructions into the instrument itself.
- Operationalizes intensity and frequency and provides an overall severity score for each item based on intensity and frequency ratings
- Anchor descriptions clarified, and behavioral exemplars provided for each severity level of each item

Manual of scoring conventions:

- Brief and user friendly
- Imbedded in the scale
- Reflects agreed-upon conventions from diverse users of the scale
- Standardizes rating conventions for each item

Structured interview guide:

- Modeled on the SIGH-D by Williams
- Semi-structured: each item begins with required probes, but additional optional probes are provided
- Additional Standardizes probes for assessing frequency and intensity

Studies: Once developed several studies were initiated to examine the GRID HAMD

Results: An initial pilot study demonstrated the ease of use of the scale

- A reliability study demonstrated good reliability for the scale
- Validity studies are being conducted in North America and Europe

Conclusions: A collaborative effort by academia, government, and industry has been able to produce a consensus method for assessing depression. This collaborative model can be utilized to develop new scales.

The full scale will be available on the poster for viewing for the first time in public.

The scale is in the public domain and will be available for download from www.iscdd.org

POSTER NO. 218

DIFFERENTIAL EFFECTS OF ANTIPSYCHOTIC MEDICATIONS ON OVERWEIGHT PEOPLE WITH SEVERE MENTAL ILLNESS IN A PSYCHOSOCIAL WEIGHT LOSS PROGRAMME

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Background/Aims: Antipsychotic induced obesity carries serious physical and psychological implications. Antipsychotic drugs vary greatly in their propensity to induce weight gain, but there is little information about whether response to a weight loss intervention varies according to the treatment.

Methods: We invited patients who were overweight, and wanted to lose weight, to participate in a weight management programme. Patients self-referred, or were referred to the service via their primary clinical teams. Patients were in and outpatients of the South London and Maudsley National Health Service (NHS) Trust (catchment popn. 520,000).

Service inclusion criteria were: DSM IV diagnosis of schizophrenia, schizoaffective disorder or bipolar illness; stably maintained on antipsychotic treatment; overweight (BMI > 25); and agreeable to participation in a weight management programme.

Exclusion criteria were: Concomitant diagnosis of eating disorder, learning disability or substance misuse; any physical problem precluding participation in a weight management programme. After screening, 44 patients were included. Local ethics approval was granted to formally audit the service.

Intervention: Patients were assessed, and given a self-report "diet diary, recording all food and drink consumed over the following week. Patients were seen within a fortnight, the "diet diary" discussed, and an individualised diet plan dispensed. They had advice on exercise and referral to the hospital gymnasium, including a visit and tour of the gym, and introduction to the gym instructor. They were seen weekly or fortnightly for three sessions of motivational interviewing. Patients were monitored monthly for weighing.

Results: 44 patients (28 f, 16 m) received the intervention. Mean (SE) baseline weight was 96.1(3.1) kg (mean (SE) baseline BMI was 33.1(.84)). Mean weight change for the whole group was -3.1kg, though there was wide variability of response (range -19kg-+8.7kg). Patients were on a variety of antipsychotic treatment, and some were also treated with mood stabilisers and antidepressants. No relationship was found between the primary antipsychotic and weight change, nor did antidepressants or mood stabilisers affect outcome.

Conclusions: The primary antipsychotic was not a determinant of response to this programme. It would appear from these data that although certain antipsychotics induce greater degrees of weight gain than others, there is no differential effect in terms of response to this psychosocial weight loss intervention.

POSTER NO. 219

EFFECTS OF MOOD STABILIZER TREATMENT ON MOOD EPISODE RELAPSE AND RECURRENCE IN BIPOLAR DISORDER

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Objective/Background: Recently completed maintenance studies have demonstrated the efficacy of both lithium and the anticonvulsant mood stabilizer, lamotrigine, in delaying subsequent mood episodes in both recently depressed (GW605) or manic/hypomanic/ mixed (GW606) bipolar outpatients. This analysis examined whether these treatments reduced relapses, recurrences or both.

Methods: 588 currently or recently symptomatic bipolar I patients (DSM-IV) were randomized to 18 months of double-blind monotherapy with lamotrigine (100-400mg/day), lithium (0.8-1.1mEq) or placebo. Efficacy outcomes (time from randomization until intervention for an emerging manic or depressive episode) were examined, both including and excluding return to the index episode during the first 60-90 days following stabilization (relapse).

Results: Both lithium and lamotrigine were effective in delaying intervention for any mood episode in the general study population. When relapses during the first 60 study days were eliminated from the analysis, both lithium and lamotrigine continued to separate significantly from placebo (median survival = 193 days), lithium (310 days) or lamotrigine (472 days). Similar results were obtained when relapses during the first 90 study days were eliminated.

Conclusion: Lithium and lamotrigine both appear efficacious against manic or depressive syndromes that re-emerge after a recent acute episode, or that recur as new episodes altogether.

Source(s) of Funding: Funding was provided by GlaxoSmithKline

POSTER NO. 220

ZIPRASIDONE VERSUS OLANZAPINE: CONTRASTS IN CHD RISK

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Objective: To examine differences in coronary heart disease (CHD) risk arising from short-term treatment with ziprasidone and olanzapine.

Methods: Hospitalized schizophrenic adults underwent 6 weeks' randomized, double-blind treatment with ziprasidone or olanzapine, with data collected at baseline and endpoint for fasting lipids and weekly for BP. A Framingham algorithm was used to calculate percentage CHD risk over 10 years in patients =30 years (per algorithm). Baseline-to-endpoint LS mean changes in age-adjusted risk by sex were compared using ANCOVA (baseline adjusted).

Results: In men =30 years, there was a significant difference in LS mean changes in TC for olanzapine vs. ziprasidone (+24.8mg/dL [n=56] and +0.52 mg/dL [n=50], respectively; p=0.004). A significant difference was also seen in LS mean changes in LDL-C for olanzapine and ziprasidone (+14.0 mg/dL [n=49] and -1.24 mg/dL [n=46], respectively; p=0.01). CHD risk in men increased by 0.8% (baseline 4.2%) with olanzapine (n=55) and decreased by 0.2% (baseline 4.5%) with ziprasidone (n=46) (P<0.05 between groups). In women =30 years, between-group differences were trending towards significance for lipid changes and CHD risk. Neither treatment had significant effects on BP.

Conclusion: In short-term treatment of men, olanzapine caused significant changes in lipid profile versus ziprasidone, with a consequent significant increase in CHD risk versus ziprasidone. These findings, coupled with those of significant weight gain with olanzapine versus ziprasidone, warrant investigation in longer-term trials.

Source of Funding: Supported by funding from Pfizer Inc.

POSTER NO. 221

REFERENCED-EEG IN THE TREATMENT OF EATING DISORDERS

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Objective/Background: rEEG is a technology that uses quantitative EEG (QEEG) findings as the independent variable to predict medication response. A database of 1,625 medication-free psychiatric patients, across a range of DSM disorders, containing QEEG findings and medication outcomes are used to derive a retrospective standard spectrum from which medication class and agent response predictions are made. We report here on rEEG-guided treatment of eating disorder patients in ongoing clinical work.

Methods: Patient characteristics are described in Figure 1. Patients in the rEEG Guided Group all had a medication-free (off all medications for at least 7 half-lives), eyes closed, awake, digital EEGs using the International 10/20 system. An artifact-free sample was Fast Fourier transformed, log-transformed to obtain Gaussianity, age-regressed, and z-transformed according to standard QEEG procedures as previously described by us. This data was compared to the database retrospective standard spectra to develop medication response predictions, which were used by a board-certified psychiatrist to treat all patients in the rEEG Guided Treatment group. Clinical outcomes were assessed by the treating psychiatrist using a modified CGI improvement scale.

Results: Results are summarized in Figure 1. Agents within six medication classes were identified from the rEEG database, including antidepressants (N=12), anticonvulsants (N = 4), lithium (1), stimulants (N=4), beta-blockers (N = 3), benzodiazepines (N = 4) and amino acids (N = 3). A seventh class, antipsychotic agents (N = 3) was prescribed empirically.

Conclusion: rEEG-guided therapy demonstrated a high rate of effective treatment outcomes (70% in anorexia, 80% in bulimia), greater than one would generally expect from most clinical settings with a primarily treatment-refractory patient population. These results warrant a randomized, controlled study.

Source(s) of Funding: No outside support was used in the conduct of this study.

POSTER NO. 222

POST-HOSPITALIZATION CONTINUITY OF ANTIPSYCHOTIC PHARMACOTHERAPY AMONG MEDICAID RECIPIENTS

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Objective/Background: Multiple factors may contribute to the relapse of patients with schizophrenia, however medication status is consistently the most robust. Robinson demonstrated a 5-fold increase in relapse risk in first episode patients who discontinued antipsychotic medication 1. Additionally, chronic patients are expected to relapse at a rate of approximately 10% per month after discontinuing medication 2. Much of the effort to improve outcomes for patients with schizophrenia have focused on improving adherence to implemented medication regimens. In our current healthcare environment, emphasis on continuity of care in the transition from inpatient to the community is extremely important. Discontinuous pharmacotherapy is expected to contribute to poor patient outcomes including relapse. In this study we evaluated the continuity of antipsychotic pharmacotherapy post-discharge among Medicaid recipients in Kentucky.

Methods: A retrospective evaluation of the continuity of pharmacotherapy of all Medicaid-enrolled clients with an acute hospitalization (< 60days) at any of the three state psychiatric hospitals during fiscal year 2002. Demographic, inpatient pharmacy, and hospitalization data were obtained from the state information system. Inpatient variables included race, sex, age, diagnosis, length of stay, and number of hospitalizations. Outpatient claims for medication prescriptions filled and/or refilled post discharge, timeliness of obtaining medication refills, and outpatient visits with a mental health provider were obtained from the Medicaid Claims Database. Discontinuous pharmacotherapy was defined as 1) a change in antipsychotic from that prescribed at discharge, 2) discontinuation of antipsychotic while continuing with mental health outpatient visits, or 3) the addition of a second antipsychotic.

Results: There were a total of 1653 eligible discharge episodes during the study period. While 93% (1537/1653) of patients had at least one medical service claim during the first 60 days post-discharge, only 45% (744/1653) had a claim for an antipsychotic prescription. Approximately 30% of patients had their antipsychotic changed post-discharge.

Conclusion: Most patients receive follow-up care post-discharge, however this does not equate with continued antipsychotic therapy.

Source(s) of Funding: Centers for Disease Control and Prevention

POSTER NO. 223

DOSE-RANGING STUDY OF ARIPIPRAZOLE IN PATIENTS WITH ALZHEIMER'S DEMENTIA

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Objective: To evaluate fixed-dose aripiprazole for the treatment of institutionalized patients with psychotic symptoms associated with Alzheimer's dementia (AD).

Methods: This multicenter, double-blind, placebo-controlled trial randomized 487 institutionalized patients with psychotic symptoms associated with AD to treatment with fixed doses of aripiprazole or placebo for 10 weeks. Aripiprazole was dosed at 2, 5 or 10 mg/day. Efficacy assessments included the NPI-NH Psychosis subscale (primary variable) and Total scale, BPRS, CGI, and Cohen-Mansfield Agitation Inventory (CMAI) score.

Results: Aripiprazole-treated patients (10 mg/day) showed significant improvement relative to placebo in the NPI-NH psychosis subscale at endpoint (-6.87 vs -5.13; P=0.013). Other measures where aripiprazole (10 mg/day) showed significant improvements at endpoint included the NPI psychosis response rate (65% vs 50%, P=0.019), changes in CGI Severity (-0.72 vs -0.46, P=0.031) and BPRS total scores (-7.12 vs -4.17, P=0.030). The BPRS Core and CMAI scores improved with both the 10 mg/day and the 5 mg / day dose. The occurrence of AEs was comparable between aripiprazole and placebo. The incidence of EPS-related AEs was 6% with placebo and 7% with aripiprazole.

Conclusions: Aripiprazole treatment resulted in significant improvements in symptoms of psychosis, agitation and clinical global impressions. Aripiprazole was well tolerated in this population.

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POSTER NO. 224

MALE SCHIZOPHRENIC PATIENTS HAVE IMPAIRMENT IN PROCESSING SPATIAL INFORMATION FROM DISSOCIATED SPATIAL FRAMES OF REFERENCE

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Objective/Background: It is known from animal studies that the hippocampus is involved in organizing spatial behavior by integrating information from several spatial reference frames. In this project we tested the hypothesis that schizophrenic male patients are impaired in their ability to organize spatial behavior, specifically when spatial cues are continuously dissociated into separate reference frames.

Methods: Fourteen symptomatically stable male schizophrenics and 13 age matched male control subjects were studied. We utilized a validated computer-based navigation task to test whether male schizophrenic patients are less able to organize responses to spatial stimuli in two dissociated spatial frames of reference. The computer task involved viewing a ten-sided polygonal "arena" projected onto a wall. The subject must identify (hit) a target that is shown at the beginning of each trial and is then hidden. The target is anchored to the arena, which may be stable (Phase 1,3,5) or rotating (Phase 2,4,6). Two interference landmarks can be either absent (Phase 1,2), or anchored to either stationary (Phase 3) or the rotating frame (Phase 4). The arena-target and the interference landmarks may be in the same frame of reference (Phase 3,4) or in a dissociated frame of reference (Phase 5,6).

Results: Multivariate analysis with phase as a repeated measure and age as a covariate demonstrated a significant group by phase interaction ($F=3.316$; $p=0.019$). Posthoc tests revealed that patients had a poorer performance than controls in Phase 5, i.e., dissociation with rotation of arena and target while interference objects remained stable ($t=-2.3$, $p=0.03$), but not in Phase 3, i.e. rotation of arena, target and interference objects without dissociation ($t=-0.27$, $p=0.79$).

Conclusion: There is a disturbance of the ability to organize spatial stimuli from two dissociated spatial frames of reference in male schizophrenic patients. This is a cognitive deficit in schizophrenia patients that has not been previously reported.

Source(s) of Funding: none

POSTER NO. 225

DRUG SENSITIVITY IN THE AGING BRAIN AND SUBCLINICAL STRUCTURAL BRAIN DISEASE

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Background: Elderly patients appear more likely than younger adults to experience side effects to psychotropic medications, which often leads clinicians to modify dose titration schedules for older patients ("start low and go slow"). While this strategy may minimize adverse events, patients will be under-treated for a prolonged time because we do not have a robust method for differentiating between those in need of gradual dosing and those who can tolerate standard regimens. In this project, we examined the relationship between sensitivity of the aging brain to anticholinergic challenge and volumes of specific types of subclinical structural brain disease (SSBD (Cook et al., 2002)). to clarify the pathophysiologic contributions of structural damage to drug sensitivity.

Methods: Elderly (=65 y.o.), dementia-free community-dwelling subjects (n=9, mean age 70) underwent structural MRI, and had a quantitative EEG (QEEG) recording while receiving an anticholineric challenge via an intravenous bolus of scopolamine (0.003mg/kg). Transaxial MRI scans were obtained with a GE Signa 1.5T scanner (double-echo sequence TE 3000, TR1 16, TR2 80, 3mm continuous slices, 256x256 window). Segmentation was performed with the MRX system (Cline et al., 1990) and volumetric measurements of perventricular hyperintensities (PVH), deep white matter hyperintensities, cortical atrophy and central atrophy were made, as well as of grey and white matter and CSF. QEEG recordings were acquired with the QND System using 36 scalp electrodes (International 10-20 System), with SR 256 samples/sec/channel (0.3-70 Hz passband). Drug sensitivity was assessed as change in alpha relative power (pre-infusion baseline to 30 minutes post infusion).

Results: Volume of PVH was significantly correlated with decrease in alpha power in response to scopolamine ($r=-0.7$, $p<0.05$), but other SSBD measures (central and cortical atrophy; deep white matter hyperintensities) showed no significant correlation with infusion-related QEEG changes.

Conclusions: In this preliminary examination, CNS sensitivity to a standardized anticholinergic infusion was related to volume of PVH, but not to the volume of other SSBD types. Prior work has shown that the volume of PVH and its progression over time are related to cerebrovascular health factors (Cook et al 2002, 2004). Our findings may clarify the mechanisms that link these cerebrovascular risk factors with increased sensitivity to side effects in the elderly.

Funding Source: NIMH (K08 MH001483)

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POSTER NO. 226

RELATIONSHIP OF ANTIPSYCHOTICS TO NEW CASES OF DIABETES MELLITUS

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Objective/Background: This study aims to detect the increase in risk of diabetes mellitus from exposure to second generation antipsychotics (SGAs) (clozapine, risperidone, olanzapine, quetiapine) compared to first generation antipsychotics (FGAs) among seriously and persistently mentally ill patients in a large state hospital system.

Methods: Using a case-control study design, and using new prescription of an anti-diabetic medication to identify new cases of diabetes mellitus, odds ratios were calculated for exposure to different antipsychotics. Cases and controls were identified for the period January 1, 2000 to December 31, 2002 using a database containing drug prescription information from the in-patient facilities operated by the New York State Office of Mental Health. Eight controls for each case were matched by calendar year, length of observation period, ethnicity, age group, and diagnosis. Among 15,563 unique patients receiving antipsychotics, 7,546 met our entry criteria of being hospitalized at least 60 days and not prescribed anti-diabetic medication in the past as documented in the database.

Results: Using conditional logistic regression and adjusting for gender and age, statistically significant elevations in risk were observed for patients receiving more than one SGA (OR=3.26, 95% CI=1.76-6.05), clozapine (OR=2.14, 95% CI=1.09-4.20) or quetiapine (OR=4.10, 95% CI=2.06-8.17), compared to exposure to FGAs alone. Although not statistically significant, odds ratios for olanzapine (OR=1.59, 95% CI=0.87-2.90) and risperidone (OR=1.59, 95% CI=0.85-2.99) were also elevated.

Conclusion: Exposure to multiple SGAs, clozapine or quetiapine increased the risk of developing diabetes mellitus, as defined by receiving a new prescription for an anti-diabetic agent.

Source(s) of Funding: Industry funding of this study: none. Funding of the database has been obtained through unrestricted grants from Eli Lilly & Co., the Janssen Research Foundation, and Pfizer, Inc.

POSTER NO. 227

EFFECTS OF PNP-12 ON COGNITIVE PERFORMANCE IN AGE-ASSOCIATED MEMORY IMPAIRMENT

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Background: Age-Associated Memory Impairment (AAMI) is a diagnostic term adopted by an NIMH Workgroup in 1986 to describe healthy adults 50 years of age and older who are not demented but who present with both subjective and objective evidence of memory loss. PNP-12 is a derivative of Cerebrolysin, a brain derived peptide preparation shown to have multiple neurochemical and neurophysiological effects. Cerebrolysin is widely used outside the United States for treating profound neurological disorders including brain trauma and Alzheimer's Disease but the compound must be administered through multiple intravenous infusions. PNP-12 is a derivative of Cerebrolysin that is less potent but is administered orally. AAMI is logical indication for PNP-12 because the compound diminishes cognitive deficits in aged animals and has a very favorable toxicology profile. This is the first controlled trial of PNP-12 in AAMI.

Methods: Subjects were 54 males and females 50 years of age and older who met criteria for AAMI. The study was designed as a fully randomized, double-blind, parallel groups study in which subjects were randomly assigned on a 2:1 basis to PNP-12 or placebo. Cognitive assessments were conducted at baseline and after 30 days of treatment. The primary outcome measure was a Memory Score derived by summing scores on three cognitive subtests (Word Recall, Word Recognition and Delayed Word Recall) of the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog). Secondary outcome measures included the Sydrom Kurz Test (SKT) and a clinical rating scale.

Results: Performance of subjects treated with PNP-12 was superior to that of subjects treated with placebo ($P<.01$) at the conclusion of treatment on the primary outcome measure, as well as the Total SKT Score and the Total Score on the global rating scale. There were no differences between PNP-12 and placebo that approached statistical significance on adverse events.

Conclusions: PNP-12 appears to be a promising compound for treating AAMI, a condition that occurs so frequently in later life as to be considered "normal." Numerous drug trials have been undertaken in this indication but in nearly every case there was either no evidence of efficacy or adverse events were noted that precluded further development of the compound. Further studies with PNP-12 will establish the range of its clinical value.

Source of Funding: EBEWE Pharma

POSTER NO. 228

QUETIAPINE VERSUS HALOPERIDOL DECANOATE FOR LONG-TERM TREATMENT OF SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

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Objective/Background: Studies comparing conventional and atypical antipsychotics suggest that the atypical agents may have advantages in long-term treatment. However, few studies have compared oral formulations of atypical agents to long-acting depot formulations of conventional agents. The objective of this study was to compare the duration of exacerbation-free survival and ratings of antipsychotic efficacy and tolerability in patients with schizophrenia or schizoaffective disorder during long-term maintenance with oral quetiapine versus intramuscular haloperidol decanoate.

Methods: Thirty-five patients from clinics at UCLA and Stanford University with schizophrenia or schizoaffective disorder were randomly assigned to maintenance with quetiapine or haloperidol decanoate. Treatment with each agent was open label and at the optimal dosage for each individual. Assessments using the Positive and Negative Syndrome Scale (PANSS), the Simpson-Angus Scale (SAS), and the Barnes Akathisia Scale (BAS) were carried out by blinded raters. A general linear mixed model repeated measures analysis of covariance was used, with change scores for dependent variables computed with the baseline score as covariate.

Results: Of 35 individuals who gave consent, 6 declined to participate when they were informed of their assigned treatment; 4 of the 6 refusals were for assignment to haloperidol decanoate. The decline in numbers over the course of the study reflects the cumulative rate of symptomatic exacerbation. At the first postbaseline assessment (week 4), data were collected from 23 exacerbation-free patients (15 in the quetiapine group, 8 in the haloperidol decanoate group). By the final assessment (week 48), the number of patients remaining in the study had fallen to 10 (5 in each group). We found no between-treatment differences in the rate of exacerbation-free survival or survival for all reasons over the course of 1 year. We did find greater improvement in negative symptoms on the PANSS, as well as greater reductions in rigidity on the SAS and akathisia on the BAS, in the patients assigned to quetiapine. Mean doses at the end of the study were 493 mg/d for quetiapine and 170 mg/28d for haloperidol decanoate.

Conclusion: In this randomized controlled study, examining outcomes at 1 year, an oral atypical antipsychotic, quetiapine, was comparable to an injectable conventional agent, haloperidol decanoate, in preventing relapse. Oral antipsychotic administration was as effective as administration of an antipsychotic by injection. Quetiapine was advantageous in reducing negative symptoms and motor side effects.

Source(s) of Funding: The research presented was supported by the Department of Veterans Affairs Medical Research Service and by AstraZeneca Pharmaceuticals LP.

POSTER NO. 229

PHARMACOTHERAPY RECEIVED BY INDIVIDUALS WITH BODY DYSMORPHIC DISORDER

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Background: Although body dysmorphic disorder (BDD) is a relatively common and impairing disorder, treatment research is still limited. In particular, no studies have assessed pharmacotherapy received by individuals with BDD in nonspecialty settings.

Methods: We assessed pharmacotherapy received by 151 individuals with DSM-IV BDD participating in a prospective study of the course of BDD (70% female, mean age=30.71, SD=11.53). The 151 subjects were referred to the study from a wide variety of sources and had not been treated in a BDD specialty program. At the intake interview, subjects provided information on current and past medications received and response of BDD symptoms to these medications (assessed with the CGI). Current BDD severity was assessed with the BDD-YBOCS, a reliable and valid measure.

Results: 73% (N=110) of subjects had ever received psychotropic medication, and 51% (N=77) were currently receiving psychotropic medication. The most common type of medication ever received was an SRI (67%; N=101), followed by benzodiazepines (28%; N=42) and other antidepressants (27%; N=41). Among subjects who had taken psychotropic medication (N=110), the mean number of medications received was 5.01, SD=4.52 (range=1-19), and the mean number of medication treatment sessions was 37.23, SD=54.33 (range 1-300). Although 80% of subjects considered BDD their most problematic disorder (compared to any comorbid disorders), only 51% of subjects revealed their BDD symptoms to their pharmacotherapist, and only 22% of pharmacotherapists focused on BDD in treatment. Although it is somewhat unclear what constitutes a minimally adequate SRI trial for BDD, only 37% (N=41) of lifetime SRI trials were considered minimally adequate for BDD (i.e., a relatively high dose and at least a 12-week trial). To increase the power of analyses examining the relationship of SRI trial adequacy to BDD response and current BDD severity, we included 49 additional study subjects who had ever been treated by the first author. Minimally adequate SRI trials led to greater improvement in BDD symptoms than inadequate SRI trials ($p<.0001$). Subjects currently receiving a minimally adequate SRI trial had significantly lower BDD-YBOCS scores than those currently receiving an inadequate SRI or no SRI ($p=.0008$).

Conclusion: These findings are limited by the fact that most treatment data were obtained retrospectively, and most subject reports were not corroborated. Nonetheless, we found that a high proportion of individuals with BDD receive psychotropic medication, primarily SRIs. However, only a minority received what is generally considered a minimally adequate SRI trial for BDD. More adequate SRI treatment was associated with greater improvement in BDD and less severe current BDD symptoms.

Source of Funding: Supported by NIMH grant R01 MH60241 to Dr. Phillips.

POSTER NO. 230

LONG-TERM COGNITIVE IMPROVEMENT IN PATIENTS SWITCHED TO ZIPRASIDONE

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Objective/Background: Memory impairment in schizophrenia is associated with functional impairment. We examined improvement in memory functions associated with ziprasidone in patients switched from other antipsychotics.

Methods: Three open-label, flexible-dose continuation studies enrolled patients who completed 6-week trials wherein they had been switched to ziprasidone from conventional antipsychotics, risperidone, or olanzapine due to suboptimal antipsychotic efficacy or tolerability. Learning and memory were assessed at last visit with the Rey Auditory Verbal Learning Test (RAVLT). Changes from the core study baseline to endpoint in the ITT population are reported.

Results: Overall, median treatment duration was 215 days. Patients in all three studies demonstrated significant improvement in multiple components of the RAVLT. Patients switched from conventional antipsychotics (n=71) demonstrated improvement in performance on first learning trial ($P<0.001$), Total Learning over five learning trials ($P<0.05$), and Long Delay Recall ($P<0.05$) components. Patients switched from olanzapine (n=71) exhibited improvement in Trial One Performance ($P<0.0005$), Total Learning ($P<0.0001$), and Long Delay Recall ($P<0.005$), Patients switched from risperidone (n=43) improved significantly on Total Learning ($P<0.05$) and Long Delay Recall ($P<0.01$).

Conclusion: Patients switched to ziprasidone may experience improvement in learning and memory over a long-term period. The functional consequences of the improvements are yet to be determined.

Source(s) of Funding: Supported by funding from Pfizer Inc.

POSTER NO. 231

A CHART-REVIEW STUDY OF SRI CONTINUATION TREATMENT VERSUS DISCONTINUATION IN BODY DYSMORPHIC DISORDER

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Background: Available data indicate that body dysmorphic disorder (BDD) often responds to SRIs, perhaps selectively. However, to our knowledge, no studies have examined relapse with continuation versus discontinuation of an efficacious SRI.

Methods: We reviewed the clinical records of 48 patients with DSM-IV BDD (69% females, mean age=32.5 ± 11.6) who responded to an SRI and were then clinically followed for an additional 6 months. Subjects must have responded to an acute SRI trial of at least 12 weeks, with much or very much improvement on the CGI at 2 consecutive clinic visits at least 1 month apart. (The second of these ratings was the first continuation phase treatment rating.) We assessed the status of BDD symptoms at each clinic visit for the next 6 months for subjects who continued the efficacious SRI (n=25) versus those who discontinued it (n=23). The primary outcome measure was the BDD-PSR (Psychiatric Status Rating scale), a reliable 7-point scale that reflects whether BDD symptoms are in full remission, partial remission, or meet full DSM-IV criteria for BDD. Relapse of BDD was defined as a worsening of PSR score by at least 2 points plus meeting full DSM-IV criteria for BDD. SRI trials were included only if patients were not receiving any other psychotropic medication or CBT.

Results: Allowing for censoring, life table analysis estimated that the proportion of patients in the SRI discontinuation group who relapsed over 6 months of follow-up was 87% (n=20) compared to 8% (n=2) in the SRI continuation group. Relapse occurred significantly earlier in the SRI discontinuation group than in the SRI continuation group (log rank test=36.05, df=1, p<.0001). The median time to relapse in the SRI discontinuation group was approximately 75 days. Forty percent (n=10) of subjects who continued the SRI for 6 months had further improvement in BDD symptoms (i.e., at least 1 point improvement on the BDD-PSR between the beginning and end of the continuation phase).

Conclusions: Study limitations include its chart-review nature, relatively small sample size, lack of randomization, and lack of patient and rater blinding to treatment condition. Nonetheless, we found that patients who discontinued an efficacious SRI had a significantly earlier time to relapse and higher relapse rate than those who continued an efficacious SRI over 6 months of follow-up. In addition, 40% of SRI responders who continued an efficacious SRI for 6 more months had further improvement in BDD symptoms.

Source of Funding: NIMH K24 MH63975 to Dr. Phillips

POSTER NO. 232

GLUCOSE METABOLISM IN SCHIZOPHRENIA PATIENTS TREATED WITH ATYPICAL ANTIPSYCHOTICS: A FREQUENT SAMPLED INTRAVENOUS GLUCOSE TOLERANCE TEST AND MINIMAL MODEL ANALYSIS

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Objective/Background: While the incidence of new-onset diabetes mellitus appears to be increasing in schizophrenia patients treated with certain atypical antipsychotic agents, it remains unclear whether atypical agents are directly affecting glucose metabolism or simply increasing known risk factors for diabetes. As a first approach to the examination of drug effects upon glucose metabolism, we chose to do a cross sectional design study examining the two drugs most clearly implicated (clozapine and olanzapine) compared to the atypical agent least implicated (risperidone) using a frequent sampled intravenous glucose tolerance test (FSIVGTT) and minimal model analysis.

Methods: Matched, non-obese (BMI < 30 Kg/m²) schizophrenia subjects treated with clozapine, olanzapine, or risperidone were recruited from an urban mental health clinic and evaluated at Massachusetts General Hospital using a FSIVGTT and Bergman's Minimal Model Analysis.

Results: Fasting serum insulin concentrations differed between groups (DF=33, F=3.35, p=.047) with significant differences between both clozapine and risperidone (DF=33, t=2.32, p=.027) and olanzapine and risperidone (DF=33, t=2.15, p=.039). There was a significant difference in insulin sensitivity index (SI) between groups (DF=33, F=10.66; p=.0003) with clozapine and olanzapine subjects exhibiting significant insulin resistance compared to risperidone-treated subjects: clozapine vs. risperidone (DF=33, t=-4.29; p=.0001); olanzapine vs. risperidone (DF=33, t=-3.62; p=.001). Insulin resistance calculated by the HOMA-IR also differed significantly between groups (DF=33, F=4.92, p=.014); clozapine vs. risperidone (DF=33; t=2.94; p=.006) olanzapine vs. risperidone (DF=33; t=2.42; p=.02). Both clozapine and olanzapine showed elevations in HOMA-IR compared to risperidone. There was a significant group effect difference in glucose effectiveness (SG) (DF=30, F=4.18, p=.025) and between groups comparing clozapine to risperidone (DF=30, t=-2.59, p=.015). Comparing olanzapine to risperidone (DF=30, t=-2.34, p=.026) was also significant.

Conclusion: Our findings suggest that non-obese clozapine- and olanzapine-treated subjects displayed significant insulin resistance, compared to risperidone-treated subjects.

Source(s) of Funding: This study was supported by a National Institute of Health (NIH/NCRR) Grant 5MO1RR01066-24 (General Clinical Research Center), New Investigator Award, NARSAD, and Janssen Pharmaceutica.

POSTER NO. 233

SEXUAL FUNCTION AND PROLACTIN LEVELS: A RANDOMIZED DOUBLE-BLIND 12-WEEK STUDY OF QUETIAPINE, RISPERIDONE OR FLUPHENAZINE

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Objective/Background: Sexual dysfunction, often iatrogenic, is common in people suffering from severe mental disorders such as schizophrenia. It has been implicated as a major reason for noncompliance with antipsychotic medications and known to be one of the areas of treatment with the most unmet needs.

Methods: After a four-week trial of conventional antipsychotics or olanzapine, 39 schizophrenia subjects were randomized to quetiapine (400 mg/day), risperidone (4 mg/day) or fluphenazine (12.5 mg/day) in a double-blind fashion for 12 weeks.

Results: Twenty-seven (69%) of these people (85% male, similar among groups) completed baseline and endpoint ratings of the Changes in Sexual Function Questionnaire (CSFQ), the Prolactin-Related Adverse Event Questionnaire (PRAEQ) and had prolactin levels drawn. Endpoint prolactin levels were 50.62 (40.43) mg/dl, 24.40 (18.46) mg/dl, and 8.18 (4.41) mg/dl for risperidone (N=12), fluphenazine (N=9) and quetiapine (N=6), respectively ($F=7.5, df=2, p=0.005$, controlling for sex). Orgasm quality/ability improved significantly for quetiapine as compared to fluphenazine and risperidone ($F=4.41$, $df=2$, $p=0.033$). Seventy-eight percent of patients on fluphenazine reported sexual dysfunction whereas only 42% and 50% of risperidone and quetiapine reported sexual dysfunction. Forty percent of patients on quetiapine reported a subjective improvement in sexual functioning, as did 55% on risperidone. Conversely, only 13% of fluphenazine subjects reported any improvement. Hormonal problems (menstrual problems, gynecomastia, galactorrhea) were predominately observed in risperidone-treated subjects.

Conclusion: Overall, quetiapine was associated with a normalization of prolactin levels and had the greatest benefits among these drugs regarding sexual functioning.

Source(s) of Funding: Stanley Medical Institue and National Institutes of Mental Health. AstraZeneca and Janssen supplied medication for the study

POSTER NO. 234

PREDOMINANCE OF PSYCHIATRIC-BASED REASONS FOR ANTIPSYCHOTIC TREATMENT DISCONTINUATION

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Objective/Background: This research was conducted to better understand the phenomenon of antipsychotic treatment discontinuation and to provide insight into overall treatment effectiveness.

Methods: This was a post hoc, pooled analysis based on four randomized, double-blind clinical trials that had a duration of 24-28 weeks. The 4 studies included 822 olanzapine-treated patients and 805 patients treated with risperidone, quetiapine or ziprasidone.

Results: Adverse events related to worsening in psychiatric symptoms accounted for 50% (100/200) of all adverse events leading to treatment dropouts, with worsening in psychotic disorder (35/200) and suicide (completed/attempt/ideation, 18/200) being the most frequent events. Most decisions of discontinuation due to lack of efficacy were made based on patient perception (132/164). Clinical rating scales showed patients who discontinued due to lack of efficacy received no relief of their psychiatric symptoms.

Conclusion: This research demonstrated that worsening of underlying psychiatric symptoms as well as patients' perception of their failure to improve overwhelmingly contribute to treatment discontinuation, which can threaten patient well-being with the morbid consequences of illness exacerbation. Better understanding of what causes discontinuation may provide a strategy to improve patient engagement in long-term therapy and to increase patient access in realizing the goals of an effective treatment.

Source(s) of Funding: Eli Lilly and Company

POSTER NO. 235

RILUZOLE: AN INVESTIGATION OF THE ANTIDEPRESSANT EFFICACY OF AN ANTIGLUTAMATERGIC AGENT WITH NEUROTROPHIC PROPERTIES

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Background: Given the significant morbidity and mortality associated with major depression, there is a clear need to develop novel and improved therapeutics. Preclinical studies suggest that antidepressants may exert indirect effects on the glutamatergic system, in a time frame consistent with their therapeutic effects. Lamotrigine, which, among other effects reduces glutamate release, also has antidepressant effects, and a recent pilot study suggested that NMDA antagonists may have antidepressant effects. Together, the data suggest that medications which directly reduce glutamatergic neurotransmission, may represent a novel class of antidepressants. We have therefore investigated the effects of Riluzole, an antiglutamatergic and neuroprotective agent, currently used to treat Amyotropic Lateral Sclerosis (ALS).

Methods: Inclusion criteria included males and females ages 18-70 years, DSM-IV major depression recurrent without psychotic features, previous antidepressant treatment, and a MADRS score of 20. There was no exclusion for history of treatment-resistance. Subjects with major medical or neurological illnesses were excluded. After a one-week drug-free period, patients received Riluzole 50- 200mg daily for 6 weeks and were evaluated on a weekly basis. The MADRS was the primary measure of efficacy.

Results: Nineteen patients (9 men and 10 women; mean age=43.1±11.7 years) received riluzole at a mean dose of 168.8±37.2 mg/day for a mean duration of 5.4±3.7 weeks. 53% of subjects were classified as Stage 2 or greater of treatment-resistance (Stages I=47%, II=31%, III=11%, IV=0%, and V=11%). 68% of subjects completed the trial. Dunnett's multiple range test was used to compare weekly ratings to baseline. The analysis showed significant improvement on weeks 3 through 6 for all patients ($F=5.44$, $p=0.007$) and weeks 2 through 6 for completers ($F=6.70$, $p=0.004$). Response rates (50% decrease in MADRS) at week 6 for all patients and completers was 32% and 46%, respectively. Remission rates (MADRS <10) at week 6 for all patients and completers was 21% and 31%, respectively.

Conclusions: Although preliminary, these results indicate that riluzole may indeed have antidepressant properties in some patients and that double-blind placebo-controlled studies with this agent are warranted.

Source of Funding: This study was conducted at and supported by the National Institute of Mental Health in Bethesda, MD.

POSTER NO. 236

DETERMINING OPTIMUM MEDICATION IN SCHIZOPHRENIC PATIENTS: DEVELOPMENT OF A STATISTICAL MODEL

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Objective/Background: This study's purpose was to build and validate models predicting the likelihood of treatment response to olanzapine and risperidone among schizophrenics participating in clinical trials.

Methods: Data from two randomized, double-blind clinical trials comparing olanzapine to risperidone were pooled. Separate models were developed for subjects randomized to olanzapine or risperidone. Baseline independent variables present in both trials were included as predictors of treatment response (>20% reduction in PANSS score). Treatment groups were partitioned at random into model development (70%), and validation (30%) samples. Classification trees were used to identify baseline variables important for discriminating responders from non-responders. These variables were used to build logistic regression models predicting treatment response likelihood for each therapy. Models were validated on the 30% of cases reserved for this purpose.

Results: Classification trees identified different variables as important in predicting response, depending on treatment group. The logistic model for olanzapine correctly classified 64.9% of cases' response status (Kappa=0.29, "fair" agreement in predicted v. observed response, $p<.05$) in development data, and 0.37 ($p<.05$) in validation data. The risperidone model resulted in 69.2% classification agreement (Kappa=0.39, "fair" agreement, $p < .05$) in training data and 0.28 ($p<.05$) in validation data.

Conclusion: Our findings support the feasibility of estimating likelihood of response to antipsychotic medications using models built from clinical trial data, and indicate that different baseline characteristics contribute to response for different agents. Further study is needed to determine the implications and value of such predictions, and to further assess generalizability outside trial settings.

Source(s) of Funding: Eli Lilly and Company

POSTER NO. 237

ZIPRASIDONE: LONG-TERM POST-SWITCH EFFICACY IN SCHIZOPHRENIA

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Objective: To evaluate ziprasidone's long-term efficacy and tolerability in schizophrenic outpatients switched from other antipsychotics.

Methods: Three open-label, flexible-dose continuation studies enrolled completers of 6-week trials initially switched to ziprasidone from conventional agents, olanzapine, or risperidone. Primary efficacy variables were changes to endpoint from core baseline in two measures: Positive and Negative Syndrome Scale (PANSS) Total and Clinical Global Impression of Severity (CGI-S). Data were analyzed by paired t tests in the intent-to-treat (ITT [LOCF]) and completer populations.

Results: Overall median treatment duration was 215 days (range 7-824 days). Median dosage at the penultimate treatment day was 120 mg/d. In those switched from conventionals, mean PANSS Total score improved significantly in the ITT population (n=71; -6.3 [P<0.01]) and in completers (n=30; -10.1 [P<0.01]); CGI-S score improved significantly in both the ITT population (-0.4 [P<0.001]) and in completers (-0.7 [P<0.0001]). In patients switched from olanzapine (n=71), completers (n=25) exhibited significant improvements in PANSS Total score (-10.0 [P<0.01]) and CGI-S score (-0.4 [P<0.05]). In patients switched from risperidone (n=43), completers (n=17) also exhibited significant improvements in PANSS Total score (-10.9 [P<0.05]) and CGI-S score (-0.9 [P<0.001]). Ziprasidone was well tolerated, with insomnia alone having an incidence >10% in all three switch groups. No patient in any group had a QTc interval >500 msec.

Conclusions: Schizophrenic outpatients switched to ziprasidone from conventional antipsychotics, olanzapine, and risperidone demonstrated long-term improvement in symptoms and illness severity. Ziprasidone was well tolerated.

Source of Funding: Supported by funding from Pfizer Inc.

POSTER NO. 238

THE RELATIONSHIP BETWEEN COGNITIVE MEASURES AND FUNCTIONAL OUTCOMES IN SCHIZOPHRENIA

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Objective/Background: Cognitive impairment has an important impact on clinical outcome in schizophrenia and schizoaffective disorder. To examine the relationship between cognitive measures and functional outcomes in these patients, data on cognitive functioning from an ongoing study of patients treated with long-acting injectable risperidone are being gathered.

Methods: Cognition, functioning, quality of life, and efficacy were assessed at baseline and at 3 and 6 months of treatment with long-acting risperidone (25 or 50 mg every 2 weeks). Interim data on measures of cognition for 60 patients are currently available. Additional data on 180 patients, including preliminary analyses of functional and clinical outcomes, will be available for the meeting.

Results: Preliminary data from the 60 patients at 6 months showed significant improvements in a wide range of cognitive measures, including simple motor speed (finger tapping test total taps right, mean 11.3, $p<0.05$), attention (continuous performance test flanker version sum correct neutral, mean 3.3, $p=0.05$), executive functioning (strategic target detection test: target reaction time, mean -174.7 msec, $p<0.01$; total errors, mean -12.7, $p<0.02$; nonperseverative errors, mean -9.7, $p<0.01$), and verbal memory (working list memory total trial 1, mean 0.8, $p<0.03$; total learning, mean= 5.7, $p<0.02$). Results on these tests will be correlated with measures of social cognition, efficacy, and functioning in order to better understand the potential relationship between these variables.

Conclusion: Treatment with long-acting risperidone can improve cognitive function in stable patients with schizophrenia. The results will allow a prospective examination of the relationships between specific measures of cognition and functional outcome in patients with schizophrenia. Measures of social cognition and quality of life will also be evaluated and related to measures of cognition and clinical outcome.

Source(s) of Funding: Janssen Pharmaceutica Products, L.P.

POSTER NO. 239

DOSING OF SECOND GENERATION ANTIPSYCHOTIC MEDICATION IN A STATE HOSPITAL SYSTEM

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Objective/Background: To describe the dosing of second generation antipsychotics (clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) among inpatients in state-operated psychiatric centers in New York State, and to contrast this to dosing recommendations made in the manufacturers' product labeling.

Methods: Information on patients and their antipsychotic medication treatment was extracted from a database containing drug prescription information from the in-patient facilities operated by the New York State Office of Mental Health. The principal period covered was April 1, 2003 through June 30, 2003. Dosing trends were calculated by examining the second quarter of calendar years 1997-2003.

Results: There were marked difference in dosages used compared to the United States Food and Drug Administration-approved dosage ranges recommended in the product labeling. Specifically, the average daily dose of olanzapine was 21.9 mg (N=1463), exceeding the 20 mg maximum tested by the manufacturer. 43.6% of patients prescribed olanzapine received a daily dose greater than 20 mg. Among the patients prescribed quetiapine (N=801), 28.5% received a daily dose exceeding 750 mg. In contrast, patients prescribed risperidone (N=1287) received an average daily dose of 4.2 mg, substantially lower than the maximum of 16 mg evaluated during the registration studies, but consistent with the dose ranges recommended in the product label. Examining dose trends over time, it appears that the divergence from product label recommendations occurred gradually and is possibly reflective of additional clinical experience with patients having characteristics not normally included in registration studies.

Conclusion: Recommended dose ranges obtained during drug registration trials do not necessarily match what is used in actual clinical practice settings. Phase IV clinical trials that specifically target more difficult-to-treat patients are needed.

Source(s) of Funding: Partial support for the maintenance of the Integrated Research Database has been provided by unrestricted grants from Eli Lilly & Co., the Janssen Research Foundation, and Pfizer, Inc.

POSTER NO. 240

ADHERENCE TO CLOZAPINE: EFFECTS OF REDUCED FREQUENCY OF HEMATOLOGIC MONITORING

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Background: The FDA's Advisory Committee is currently evaluating the feasibility of monthly WBC monitoring for clozapine-treated patients. It is important to examine how a change in monitoring frequency is related to adherence with clozapine treatment, as this may have important implications if required monitoring frequency is further reduced. The study compared medication adherence of clozapine-treated individuals receiving weekly versus bi-weekly monitoring.

Method: Paid prescription claims records for clozapine from September 1, 1995 to August 31, 2001 were extracted from the Texas Medicaid database. Two groups of subjects were identified: subjects treated before and after a change in monitoring frequency, which occurred on April 1, 1998. Prescription claims records for each subject were assessed for 365 days after the initial six months of treatment, as both groups required weekly monitoring during this six-month period. Subjects discontinuing clozapine within the initial six-month period were excluded. Adherence measures included persistence, medication possession ratio, and time on clozapine. The mean index dose, mean daily dose, and mean maximum dose were calculated for each subject. All statistical tests were two-tailed, with significance defined as an alpha less than 0.05.

Results: Subjects receiving weekly hematologic monitoring had significantly higher rates of persistence and medication possession ratios, and remained on clozapine longer than subjects receiving bi-weekly monitoring. Subjects seen for weekly monitoring had significantly higher mean index clozapine doses, and this dose difference was maintained throughout the one-year observation period.

Conclusion: The results indicate that reduced monitoring frequency may contribute to decreased adherence to and persistence on clozapine. For some patients, continued weekly visits may be desirable. Current discussions of reducing monitoring frequency to monthly should be informed by this finding.

Disclosure/Source of Funding: This study was supported in part by the Texas Department of Mental Health and Mental Retardation, and a Ruth L. Kirschstein National Research Service Awards Postdoctoral Training Fellowship sponsored by the National Institute of Mental Health (N. Patel).

POSTER NO. 241

DISTRESS WITH MEDICATION SIDE EFFECTS AMONG PERSONS WITH SEVERE MENTAL ILLNESS

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Objective/Background: Most clinical trials assess "objective" side effects, those observed by a physician or elicited from physicians' inquiries. In contrast, few studies measure the distress from common side effects from the individual's perspective.

Methods: We examined self-reported distress with side effects from psychotropic medications as part of a study of consumer operated service programs among individuals with severe mental illness (N=1,822). We applied descriptive statistics to examine report of distress with medication side effects and forward stepwise logistic regression to examine whether gender, race or diagnoses predicted distress. We also examined correlations between distress with side effects and self-reported symptoms.

Results: The most commonly reported side effects listed in order of distress were embarrassment with weight gain, weight gain, dry mouth, and sedation. Among the 53% of study participants reporting embarrassment with weight gain, 74% were bothered at least moderately; of those 58% reporting weight gain, 70% were bothered at least moderately; of those 64% reporting dry mouth, 59% were bothered at least moderately; and of those 66% reporting sedation, 49% were bothered at least moderately. Study participants indicated that an average of 6.6 side effects (SD = 5.1) caused them at least some distress and an average of 2.7 (SD = 3.3) bothered them a lot.
Non-Caucasians and individuals with a diagnosis other than depression were significantly more likely to report distress with sedation; women and individuals with a diagnosis of bipolar disorder were significantly more likely to report distress with dry mouth. Women, African Americans, those with a diagnosis of schizoaffective disorder, and those with a diagnosis of bipolar disorder were significantly more likely to report distress with weight gain. Greater embarrassment with weight gain was significantly associated with feelings of self blame, loneliness, hopelessness, sadness, anhedonia, worthlessness, tiredness, having everything feel like an effort, and a lower self-reported quality of life.

Conclusion: The most distressing side effects were embarrassment with weight gain, weight gain, dry mouth, and sedation. Weight gain, which was also associated with a lower self-reported quality of life, can impact cardiovascular health and diabetes as well as self image. Dry mouth can cause soreness, ulcers, infections, and loss of teeth. That women reported more distress and embarrassment with weight gain and more distress with dry mouth is an important consideration as physicians prescribe medications with these side effect profiles. Future randomized studies should examine predictors of distress with medication side effects.

Source(s) of Funding: Public Health Service grants SM 52227, SM52332, SM52352, and SM52372 from the Substance Abuse and Mental Health Services Administration, as well as by the Connecticut Department of Mental Health and Addiction Services, Hartford and the Mental Illness Research, Education and Clinical Center of the Veterans Integrated Service Network 3.

POSTER NO. 242

EFFECT OF ANTIPSYCHOTIC CHANGE ON WEIGHT IN MINORITIES

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Objective/Background: We tested the effect of antipsychotic change to ziprasidone on metabolic parameters in African and Hispanic Americans. One out of two American adults is now overweight or obese. Being a minority, especially African and Hispanic American, having schizophrenia, or using an antipsychotic seem to increase the risk. Opposed to other, typical and atypical, antipsychotics ziprasidone, an atypical antipsychotic, has not been associated with weight gain in the general population or Caucasian patients.

Methods: Open label study in overweight (BMI>25) Hispanic and African American outpatients with schizophrenia/psychotic disorder, switching from other antipsychotics to ziprasidone, with no additional dietetic or behavioral interventions. Main outcome measures are weight and BMI at 6 and 12 weeks.

Results: We have enrolled nine patients, eight of whom contributed data to this analysis, at 6 weeks. Of these, seven lost and one gained weight. Average weight at baseline was 227 lb, mean change at 6 weeks was -6.75 lb (SD=5.2), significant (paired student's t-test -3.67, $p < 0.008$). Average BMI at baseline was 34.25, mean change at 6 weeks was -1.125 (SD=0.64), significant (paired student's t test -4.96, $p< 0.0016$).

Conclusion: These data suggest that African and Hispanic American overweight/obese patients with schizophrenia lose weight when switched to ziprasidone. If replicated in a controlled study, this finding would suggest that ziprasidone should be considered as an option in these patients

Source(s) of Funding: Pfizer Inc.

POSTER NO. 243

REVIEW OF INPATIENT USE OF ANTIPSYCHOTIC DRUGS AT McLEAN HOSPITAL BETWEEN 1989 AND 2002

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Background: The goal of this study was to examine antipsychotic medication usage at McLean Hospital in 2002, compared to findings in 1989, 1993, and 1998.

Methods: We analyzed medical and pharmacy records of McLean Hospital inpatients given an antipsychotic medication between March and May 2002 for information on diagnosis, admitting illness, use and dosing of all psychotropic agents, clinical status by discharge, and adverse effects, and compared results with similar data obtained in earlier years. Patients with primary psychotic vs. major affective disorders, based on DSM-IV criteria, were compared.

Results: We evaluated data from 344 inpatients (202 women, 142 men) presenting with psychotic (N=114, 33.1%), bipolar (N=93, 27.0%), major depressive (N=67, 19.5%), dementing (N=19, 5.5%), substance abuse (N=9, 2.6%), or other disorders (N=42, 12.2%). Since 1989 the use of atypical antipsychotic agents rose continuously to account for 88% of all antipsychotic prescriptions in 2002. As in 1998, olanzapine was the most commonly prescribed antipsychotic agent in 2002, followed by quetiapine (often in relatively low doses for indications other than psychosis), and risperidone. From a decade-high of 43% of patients in 1998, 32% were given =2 antipsychotics in 2002. The mean chlorpromazine-equivalent (CPZ-eq) total daily antipsychotic dose at discharge in 2002 was 289 ± 230 mg-a 22% decrease from 1998, and the first reversal of a trend toward rising doses from 1989 to 1998. Antipsychotic doses at discharge were significantly higher among psychotic than major affective disorder patients ($p<0.0001$), and with longer hospitalization. Significantly greater improvement in CGI and GAF scores from admission to discharge was seen among psychotic vs. major affective disorder patients ($p<0.05$). There were no significant correlations of total daily antipsychotic dose or age and clinical improvement.

Conclusions: Use of atypical antipsychotics came to dominate practice from 1989 to 2002, and their use in bipolar disorder increased from 74% of all antipsychotics in 1998 to 90% in 2002. Unexpectedly, total daily CPZ-eq antipsychotic dose and use of combinations of antipsychotics decreased between 1998 and 2002. Olanzapine was the most frequently prescribed antipsychotic among McLean Hospital inpatients in 2002 as it had been in 1998.

Funding: By grants from Astra-Zeneca, Eli Lilly, Bristol-Myers Squibb, and Pfizer Corporations (to FC), and a grant from the Bruce J. Anderson Foundation and the McLean Hospital Private Donors Fund for Neuropsychopharmacology Research (to RJB).

POSTER NO. 244

QUETIAPINE FOR AGITATION AND AGGRESSION IN BIPOLAR MANIA

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Objective: Evaluate quetiapine for treating agitation and aggression associated with mania in bipolar disorder.

Methods: Activation and Supplemental Aggression Risk subscale scores of the Positive and Negative Syndrome Scale (PANSS), and the Young Mania Rating Scale (YMRS) were analyzed in patients with bipolar I disorder (manic episode, DSM-IV) treated with quetiapine (up to 800 mg/day) as monotherapy (12 weeks) or in combination with lithium (0.7-1.0 mEq/L) or divalproex (50-100 ?g/mL) (3 or 6 weeks) in randomized, double-blind, placebo-controlled studies.

Results: Quetiapine monotherapy resulted in significantly greater improvements in Activation and Supplemental Aggression risk subscale scores compared to placebo at Day 21 ($P<0.001$) and Day 84 ($P<0.001$); quetiapine plus lithium or divalproex also resulted in improvements in both subscales that were significantly different from lithium or divalproex alone at Day 21 ($P<0.05$). Compared to placebo, quetiapine monotherapy significantly improved the Disruptive/Aggressive Behavior and Irritability items of the YMRS ($P<0.001$) at Days 21 and 84.

Conclusion: Quetiapine is effective in the treatment of agitation and aggression in patients with bipolar disorder.

Source(s) of funding: This research was supported by AstraZeneca.

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POSTER NO. 245

INSIGHT IN STABLE PATIENTS WITH SCHIZOPHRENIA RECEIVING LONG-ACTING RISPERIDONE

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Objective/Background: Lack of insight is prevalent in patients with schizophrenia and can include a lack of awareness of one's illness, symptoms, and the need for treatment. This analysis examined the relationship between insight and clinical and functional measures in a 50-week study of over 700 patients receiving long-acting risperidone, the first long-acting injectable atypical antipsychotic (Fleischhacker et al, J Clin Psychiatry, 2003).

Methods: In an open-label study, stable patients with schizophrenia/schizoaffective disorder were switched from their current treatments with typical or atypical antipsychotics to receive long-acting risperidone (25, 50 or 75 mg) every 2 weeks for up to 50 weeks. Psychotic symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS). The PANSS item G12 measures lack of insight and judgment (1 = No impairment to 7 = Extreme impairment). This analysis examined the relationship between insight scores and PANSS positive, negative, and anxiety/depression scale scores; the Clinical Global Impressions severity (CGI-S) rating; and a measure of quality of life/function (SF-36).

Results: Insight scores were available for 614 patients with baseline and at least one postbaseline assessment. Mean (±SD) insight scores improved from 2.7±1.5 at baseline to 2.5±1.5 at endpoint ($p<0.001$). Improvements in insight scores were significantly correlated with improvements in positive symptoms ($r=0.397$; $p<0.001$), negative symptoms ($r=0.369$; $p<0.001$), and anxiety/depression ($r=0.238$; $p<0.001$) and in CGI-S scores ($r=0.368$; $p<0.001$). Significant improvements in SF-36 scores for the mental component, vitality, social functioning, role-emotional, and mental health index were seen in patients with improved insight but not in patients whose insight was not improved.

Conclusion: These data suggest that changes in insight correspond to changes in multiple symptom domains. The findings also suggest a possible relationship between insight and functional status. Further analyses will examine these issues and whether a threshold exists for insight/judgment that is needed to achieve functional gains with treatment.

Source(s) of Funding: Janssen Pharmaceutica Products, L.P.

POSTER NO. 246

COGNITIVE EFFECTS OF ZIPRASIDONE IN FIRST EPISODE PSYCHOSIS: AN fMRI STUDY

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Objective/Background: Antipsychotic drug treatment of first episode psychosis may be complicated by side effects of widespread dopaminergic antagonism, including exacerbation of negative and cognitive symptoms due to prefrontal hypodopaminergia. Cognitive deficits in first episode psychosis have been well documented. Second generation antipsychotic drugs have had a big impact on treatment of early psychosis due to the lack of neurological side effects.

Methods: To elucidate the neural mechanisms of the effects of ziprasidone on attention and working memory in first episode psychosis, this study examined behavioral performance and blood-oxygenation-level-dependent regional brain activity (BOLD), using functional magnetic resonance imaging (fMRI), during a parametric 'n-back' working memory task in 10 subjects with first episode psychosis who were treated with ziprasidone. They were compared to patients who had received conventional antipsychotics. Functional MRI was carried out in these two groups of patients at baseline and 6 weeks later.

Results: The ziprasidone-treated group had significantly greater response at 6 weeks in dorsolateral prefrontal cortex, supplementary motor area and parietal cortex ($p < 0.005$).

Conclusion: These data provide the first direct evidence for enhanced prefrontal cortical function in first episode psychosis patients following treatment with ziprasidone and indicate the potential value of fMRI as a tool for longitudinal assessment of psychopharmacological effects on cerebral physiology.

Source(s) of Funding: Unrestricted educational grant from Pfizer Pharmaceuticals

POSTER NO. 247

INCREASED AMYGDALAR ACTIVATION AFTER SECRETIN ADMINISTRATION: AN fMRI STUDY

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Functional magnetic resonance imaging (fMRI) techniques have begun to map the regions of the brain that are active during learning, memory, and emotional experiences. Of these, the amygdala has emerged as one of the most critical areas for ascribing emotional significance to stimuli and influencing affective responsiveness and emotional learning. Neuroimaging studies indicate the amygdala often produces increased activation in response to affective stimuli, and is activated consistently during the perception of fearful facial expressions. fMRI investigations of affective disorders, schizophrenia and autism have reported abnormal amygdalar activation in response to facial emotions and other social stimuli. We previously measured BOLD fMRI signal change during facial affect processing in a placebo controlled double blind study in which we studied 12 healthy male subjects who were presented with three stimulus conditions: viewing happy, fearful and neutral faces before and after infusion with either secretin or placebo. To test whether treatment was associated with distinct patterns of activation, the two conditions (Pre and Post) were subjected to a subtraction analyses in SPM99 and hypotheses regarding the activation of the left and right amygdala were tested using a region of interest (ROI) approach. Subtraction of treatment minus baseline activation during the fear condition yielded significant ($p = .001$) activation in the right amygdala indicating that secretin may alter responsivity to affective stimuli. To further map the regions of the brain involved in social cognition processes, we have applied this paradigm to other regions of the brain including the prefrontal cortex, the fusiform face area and the cerebellum. We now report on the broader neurophysiological effects of secretin on brain activation in human subjects in response to affective stimuli.

POSTER NO. 248

THE GAIN ACCEPTANCE APPROACH: A NOVEL PSYCHOSOCIAL APPROACH TO SUPPORTING PATIENT ACCEPTANCE OF A LONG-ACTING INJECTABLE ANTIPSYCHOTIC

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Background: The effectiveness of any therapy depends upon the patient's success in accepting, adhering to, and maintaining prescribed treatment. Unless the patient remains sufficiently motivated to initiate and continue treatment, the therapeutic outcome will be sub-optimal. There is mounting evidence of a strong relationship between treatment acceptance, ongoing adherence and resultant treatment outcome in psychiatric illness. Positive responses to both pharmacological and psychosocial treatment are impacted by the enhancement of treatment acceptance.

Despite this evidence, adherence and acceptance of antipsychotic treatment remains particularly challenging for a variety of reasons, including: lack of patient insight into disease, treatment side effects, dosing requirements, cognitive deficits of psychotic patients, and co-morbid disorders that may increase the severity of disease symptoms and the risk of relapse. The introduction of long acting injectable antipsychotics (such as long acting risperidone), may help in removing some of these barriers to patient acceptance. Acceptance may be also further supported by the implementation of psychosocial interventions that address psychological barriers.

This study is designed to evaluate the effectiveness of a novel approach to supporting treatment that is based on the principles of Motivational Enhancement Therapy (MET). This approach, called the GAIN Acceptance Approach, is designed as a structured clinical discussion tool to address patient ambivalence to treatment.

Method: This study (known as the Schizophrenia Treatment Acceptance Response Trial or START) is designed to measure the effectiveness of the GAIN Acceptance Approach in supporting treatment acceptance and adherence in patients with schizophrenia. The study is designed to evaluate approximately 700 patients participating over a 6-week "Approach" phase and a 12-week "Treatment" phase in 275 Community Mental Health Centers in the US. As a primary measure of effectiveness, the percentage of patients accepting long acting risperidone (RISPERDAL CONSTATM) therapy at sites randomized to use of the GAIN Acceptance Approach will be compared to sites using an approach-as-usual method.

Results and Conclusion: Preliminary results indicate that the GAIN Acceptance Approach represents an innovative method that can be implemented with relative ease by all members of a patient's treatment team. Further evaluation of the results may support the hypothesis that the GAIN Acceptance Approach provides an effective method to engage clinicians and their patients into a collaborative relationship that supports acceptance of, and adherence to, treatment with a long-acting injectable antipsychotic. Likewise, the innovative study design of combining both pharmacologic and non-pharmacologic interventions may encourage others to implement further studies of this type.

Disclosure/Source of Funding: This study is funded by Janssen Pharmaceutica Products, LP

POSTER NO. 249

IM ZIPRASIDONE IN THE PSYCHIATRIC ER: EXPANDED SAMPLE

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Objective: Injectable atypical neuroleptics may supplant benzodiazepine and/or butyrophenone alternatives. Published studies of intramuscular (IM) ziprasidone excluded severe psychiatric agitation (AGIT), and agitation from alcohol (ETOH) or other substances (SUBS). We evaluated the efficacy of IM ziprasidone 20 mg in patients with severe agitation, including that from alcohol- or substance-induced intoxication, in the psychiatric ER setting.

Method: We report additional data on BARS agitation scores (min=1, max=7) and duration of physical restraints in a naturalistic Psychiatric ER study. Dosages were 20 mg for IM ziprasidone and varied for conventional IM sedatives (78% haloperidol and/or lorazepam).

Results: Baseline BARS scores were high for AGIT (N=72), ETOH (N=10) and SUBS (N=28) patients (respective means: 6.5, 6.9, 6.6; P=NS). Ziprasidone decreased agitation rapidly in AGIT, ETOH, and SUBS patients, with respective mean scores of 5.6, 5.3, and 5.8 at 15 minutes ($P<.05$), and 4.2, 4.1, and 4.1 at 30 minutes ($P<.01$). At 2 hours, respective scores were 2.6, 2.1, and 2.3 ($P<.01$). For conventional sedatives (N=9) baseline scores were 6.6, then 5.7 at 15 minutes, 4.2 at 30 minutes, and 2.9 at 2 hours ($P<.02$ vs ziprasidone). Restraint duration decreased from 91 ± 4 to 53 ± 3 minutes with ziprasidone ($P<0.01$) and varied with conventional sedatives (54 ± 14 minutes, P=NS). Of 19 EKGs, none had prolonged QTc; one dystonic reaction occurred with ziprasidone.

Conclusion: IM ziprasidone appears effective for severe agitation including that from alcohol or substance-induced intoxication. It may lead to reduced time in restraints compared with conventional agents.

Source of Funding: Supported by funding from Pfizer Inc.

POSTER NO. 250

MUTATION STUDIES OF PREGABALIN BINDING AND PHARMACOLOGY IN VIVO AT ALPHA2-DELTA PROTEINS

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Objective/Background: Pregabalin is a high-affinity specific ligands at the saturable binding site of alpha2-delta (a2-d) protein from brain tissues. Pregabalin is active in animal models of anticonvulsant activity, analgesic-like activity and models that detect anxiolytic drugs (eg, the Vogel conflict test, tail suspension test). The a2-d protein is an auxiliary subunit of voltage-gated calcium channels found in brain, and also in skeletal muscle, smooth muscle, and cardiac muscle. Despite identification of a2-d as the high affinity binding site for [3H]gabapentin in brain in 1996, the role of a2-d binding in the pharmacology of pregabalin has been uncertain.

Methods: To test this hypothesis, a single amino acid mutation was incorporated into the native a2-d type 1 protein to convert arginine 217 to alanine.

Results: This mutation reduced binding affinity for [3H]gabapentin in recombinant protein. Subsequently, the R217A mutation was incorporated into a strain of genetically altered mice that were normal in other respects. Homozygous and heterozygous R217A mutant mice had a slight reduction in potency of pregabalin for prevention of low-intensity electroshock seizures (ED50 value roughly twice that in wildtype control mice). Mutant R217A mice were insensitive to pregabalin in the formalin footpad analgesia test. Finally, mutant R217A mice were insensitive to pregabalin in the Vogel conflict test and in a tail suspension test that detects other known anxiolytic drugs.

Conclusion: These results (and other independent results with structure-activity studies of gabapentin and pregabalin structural analogues) strongly support the hypothesis that pharmacological actions of gabapentin and pregabalin require binding to the a2-d protein of forebrain. Factors that may contribute to the less complete effects of the R217A mutation on anticonvulsant action will be discussed.

Source(s) of Funding: Studies funded by Pfizer.

POSTER NO. 251

MEDICATION-SPECIFIC CORRELATES OF RELAPSE RISK IN SCHIZOPHRENIA

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Objective/Background: To identify potential correlates of schizophrenia relapse during olanzapine (OLZ) and risperidone (RIS) treatment.

Methods: In a 28-week comparison1 of OLZ (10-20mg/d; n=105) and RIS (4-12mg/d; n=94) we used logistic regression to explore correlates of relapse among patients who had responded at week 8 (W8). Response was defined as =20% improvement on PANSS and relapse as =20% worsening on PANSS and CGI-S=3.

Results: Quality of life at endpoint was the only relapse correlate found to be independent of treatment assignment. In the OLZ group, odds ratio (OR) for relapse was increased among patients with post-W8 dose reduction (OR= 5.4, p=0.02) and those with poorer work status at W8 (OR=2.5, p=0.02). In the RIS group, unexpectedly but consistent with prior research2, patients with greater positive symptom improvement from baseline to W8 subsequently were more likely to relapse (OR=1.1, p=0.02). In neither group was relapse associated with disease duration, negative symptoms, Parkinsonism, or weight gain. Overall, relapse was significantly more common (p=.004) among RIS responders (28.7%) than OLZ responders (12.4%).

Conclusion: Likelihood and correlates of relapse may vary between medications. These results should be confirmed in other studies because of their potential value to the clinical imperative of relapse prevention.

Source(s) of Funding: Eli Lilly and Company

POSTER NO. 252

SAFETY, TOLERABILITY, AND PATIENT FUNCTIONAL STATUS WITH LONG-TERM MODAFINIL IN CHRONIC SHIFT WORK SLEEP DISORDER

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Objective/Background: Shift work sleep disorder (SWSD) is characterized by excessive sleepiness during nighttime work hours and/or insomnia during daytime sleep periods. In two 12-week, double-blind, placebo-controlled studies, the wake promoting agent modafinil significantly improved wakefulness in patients diagnosed with chronic SWSD and was well tolerated. The objective of two open-label extension studies was to determine the continued safety, tolerability, and effects on functional status.

Methods: The two 12-month, open-label follow-up studies enrolled 292 patients (age range, 21-62) with excessive sleepiness and chronic SWSD (International Classification of Sleep Disorders), who had completed the two prior double-blind studies. Patients continued to work a minimum of 5 night shifts per month and were instructed to take modafinil (200 mg/day, study 1; 200 or 300 mg/day, study 2), administered 60 to 30 minutes before the start of their night shift. The effect of modafinil on functional status was assessed by the Functional Outcomes of Sleep Questionnaire (FOSQ). Safety and tolerability assessments included adverse events, clinical laboratory tests, vital signs, and physical examinations.

Results: 158 patients (54%) completed the study. Modafinil (both doses combined) improved patient functional status as observed in the total score at endpoint (mean change in FOSQ from baseline = 2.0 with a 95% confidence interval of 1.64-2.31). Improvements were also seen at endpoint for the individual domains: activity level (0.5, 95% CI 0.37-0.53), general productivity (0.4, 95% CI 0.29-0.42), intimacy (0.3, 95% CI 0.22-0.40), social outcome (0.3, 95% CI 0.23-0.42), and vigilance (0.5, 95% CI 0.42-0.59). When the FOSQ data from the two studies were analyzed separately, study 1 did not reach significance whereas study 2 demonstrated significant improvements in functional status, particularly for the 300 mg modafinil dose. Modafinil treatment was well tolerated. The most common adverse events included infection, headache, and accidental injury. Most adverse events were mild to moderate in severity. Fourteen patients (5%) withdrew from the studies due to adverse events. No clinically meaningful effects of modafinil were seen in clinical laboratory tests, vital sign parameters, and physical examinations.

Conclusion: Modafinil (200 and 300 mg/day doses combined) significantly improves patient functional status. These results are consistent with improvement in wakefulness including measures of sustained attention in the double-blind phase of these studies. Modafinil is well tolerated over time in patients with chronic SWSD.

Source(s) of Funding: Cephalon, Inc., West Chester, PA

POSTER NO. 253

MANUAL-GUIDED USE OF LONG-ACTING RISPERIDONE IN COMMUNITY-BASED SETTINGS

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Abstract: Objective-Long-acting risperidone is a new option in the treatment of patients with schizophrenia. Treatment manuals are useful tools for assisting knowledge transfer and practice standardization for newly available therapies. The objective of this study was to evaluate a treatment manual designed to optimize community-based care with long-acting risperidone (Risperdal CONSTA™). A novel application in treatment-manual assessment methodology was used to evaluate the effectiveness of this strategy.

Methods: A 12-week, open-label, multicenter study in community mental health care (CMHC) settings enrolled stable outpatients with schizophrenia or schizoaffective disorder switched from oral risperidone to long-acting risperidone. The primary objective was to assess the usefulness of, and adherence to, the long-acting risperidone manual. Patient experience also was assessed, using the Clinical Global Impression (CGI) scale; Schizophrenia Quality of Life Scale (SQLS); and measures of safety, tolerability, and patient attitude/satisfaction with treatment.

Results: Sixty patients participated in the study. Most (37, 61.7%) received 37.5 mg long-acting risperidone every 2 weeks. Seven (11.7%) received 25 mg Q 2wk and 16 (26.7%) received 50 mg Q 2wk. The mean dose was 39.4±7.6 mg Q 2 wk. Ninety percent of CMHC staff rated the treatment manual "quite a bit" or "extremely" informative. Adherence by clinicians (89% to 100%) and patients (87% fully-adherent) was excellent. Significant improvement on the CGI-Severity (CGI-S) was observed as early as Week 6 (P=0.033), and long-acting risperidone was well tolerated. More patients were satisfied with long-acting risperidone treatment (86% versus 63% with oral antipsychotics), 70% found long-acting risperidone "better" or "much better" than oral risperidone. Convenience and ease were the most frequently cited reasons favoring long-acting risperidone, and concern about pain decreased significantly over the study (P=0.041).

Conclusions: This study demonstrated the feasibility of adapting methods from psychotherapy research to develop and assess the effectiveness of a treatment manual for guiding and standardizing a new pharmacologic treatment in typical clinical practice settings. CMHC staff considered the treatment manual valuable, and both patients and staff adhered to manual guidelines. Additionally, long-acting risperidone was well tolerated, usually preferred to oral atypicals, and associated with significant clinical improvement, even in previously stable patients.

Disclosure: Supported by Janssen Pharmaceutica Products, L.P.

POSTER NO. 254

EFFICACY AND TOLERABILITY OF INDIPLON-IR FOR CHRONIC INSOMNIA: RESULTS USING BEDTIME AND MIDDLE OF THE NIGHT DOSING STRATEGIES

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Background: Indiplon, a GABAA receptor potentiator with selectivity for receptors with the alpha1 subunit, is being evaluated for the treatment of both chronic and transient insomnia. Two studies were conducted to evaluate the efficacy, tolerability, and safety of the immediate release (IR) formulation of indiplon for the treatment of insomnia using dosing at bedtime(study 1) or dosing in response to a middle of the night awakening (MOTN dosing; study 2).
Methods: Study 1: Adult patients (N=194; 66% female; mean age, 40 years) who met DSM-IV criteria for primary insomnia of at least 3 months duration completed polysomnography (PSG) screening and a placebo lead-in period, and were randomized to 5 weeks of double-blind treatment with indiplon-IR 10mg or 20mg or placebo (PBO). PSGs were performed on nights 1 and 2 (week 1), 15 and 16 (week 3), 29 and 30 (week 5). The primary efficacy endpoint was PSG assessment of latency to persistent sleep (LPS). Self-report measures included latency to sleep onset (LSO). Study 2: Adult outpatients (N=260; 71% female; mean age, 46 years) who met DSM-IV criteria for primary insomnia of at least 3 months duration, characterized by frequent and prolonged MOTN awakenings, and who completed a 2-week placebo lead-in period, were randomized to 4 weeks of double-blind treatment with indiplon-IR 10mg or 20mg, or placebo. MOTN dosing required patients to have a minimum of 4 hours of bedtime remaining. The primary endpoint was LSO post-dosing. Secondary endpoints included subjective assessment of post-dose awakening after sleep onset (sWASO), number of awakenings after sleep onset (sNAASO), total sleep time (sTST), and sleep quality. Next day sleepiness was evaluated by a 100-mm Visual Analog Scale.
Results: Both doses of indiplon-IR resulted (Table 1) in significant improvements in sleep parameters at most time-points using both a bedtime dosing (study 1) or MOTN-dosing (study 2).

Study 1: Bedtime Dosing With Indiplon-IR			
LS-mean results for 5 weeks of study treatment	Placebo (N=55-61)	Indiplon-10mg (N=57-65)	Indiplon-20mg (N=63-68)
LPS (min)			
Day 1-2 (visit 4)	36.9	27.7**	27.1*
Day 15-16 (visit 5)	40.0	30.4**	28.7*
Day 29-30 (visit 6)	40.1	29.2**	24.9**
LSO (min)			
Day 1-2 (visit 4)	72.5	49.8**	44.4**
Day 15-16 (visit 5)	62.6	57.4	44.7
Day 29-30 (visit 6)	67.5	57.2**	49.5*

Study 2: Middle Of The Night (MOTN) Dosing With Indiplon-IR			
LS-mean results for 4 weeks of study treatment	Placebo (N=86)	Indiplon-10mg (N=84)	Indiplon-20mg (N=90)
LSO (min)	45.2	36.5**	34.4**
sWASO (min)	15.5	9.8**	5.0**
sTST (min)	228.5	253.0**	277.5**
Sleep quality 1	3.81	3.31**	2.98**
Next day VAS-sleepiness[2]	44.4	40.5	38.7*

* $p<0.05$; ** $p<0.01$; 1 Rated from 1 (extremely good) to 7 (extremely poor);
[2]rated on 100-mm scale from 1 (very alert) to 100 (very sleepy)
Neither dosing strategy was associated with a difference from PBO in next day residual VAS-sleepiness. Overall, indiplon-IR was well-tolerated, with no serious adverse events reported.
Conclusions: Treatment with indiplon-IR resulted in significant improvement in sleep onset that was sustained across 4 or more weeks of treatment, whether administered at bedtime, or using MOTN-dosing. Indiplon-IR was well-tolerated in both studies, with no next-day residual effects.
Source of funding: Neurocrine Biosciences, Inc.

POSTER NO. 255

DIVALPROEX SODIUM EXTENDED RELEASE FOR ACUTE TREATMENT OF SCHIZOPHRENIA: A RETROSPECTIVE CHART REVIEW

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Objective/Background: To review the effect of Depakote ER in combination with Risperdal in the reduction of psychiatric symptoms and the length of hospitalization (LOH) in patients with schizophrenia.

Methods: We reviewed the charts of 60 consecutive patients with the diagnosis of schizophrenia, treatment in an acute inpatient facility. Patients were classified by treatment, those who where treated with the combination of Depakote ER and Risperdal versus patients treated with atypical antipsychotics alone. The primary outcome data was the Length of Hospital Stay and the effectiveness was assessed using the PANSS and the CGI.

Results: Demographic variables were similar between groups. In general the total sample has a mean age of 32.5 (23 to 48) years of age, 60% were male, 40% were Caucasians and their chronicity was 13 years. The combination group had a LOH of 8.2 days, compared to 10.9 days for the comparison group. The PANSS-Total, Positive and Excitement scores were significantly better at day 3 for the combination group. The most common adverse effects were sedation, dyspepsia and diarrhea.

Conclusion: Based on the results of this limited study, the combination of Depakote ER and Risperdal appeared to decrease the length of Hospitalization and to enhance the overall treatment outcome in patients with schizophrenia.

Source(s) of Funding: Abbott Pharmaceutical

POSTER NO. 256

LUTEAL PHASE VS. SYMPTOM-ONSET DOSING WITH ESCITALOPRAM FOR PREMENSTRUAL DYSPHORIC DISORDER: A PRELIMINARY STUDY

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Objective: To examine the efficacy and tolerability of escitalopram for symptom-onset dosing compared to luteal phase dosing for premenstrual dysphoric disorder (PMDD).

Methods: After a 3-month screen period, 27 women who met criteria for PMDD were randomized double-blind to luteal phase dosing (n=13) or symptom-onset dosing (n=14) for 3 months (10-20 mg/day). Symptoms were assessed with the 17-item daily symptom report (DSR) and the Clinical Global Index (CGI). Luteal phase and symptom-onset dosing scores were compared using logistic regression and t statistics.

Results: Total premenstrual DSR scores significantly improved from baseline in both dosing groups (P<0.001)with no difference between the luteal and symptom-onset dosing regimens. The decrease in DSR scores at endpoint (LOCF) was 57% and 51% in the luteal and symptom-onset groups respectively. Clinical improvement (DSR decrease > 50% from baseline) was reported by 74% of the treated women. When symptom severity at baseline (median split) was examined with treatment response, the higher severity group was less likely to improve compared to the lower severity group with symptom-onset dosing (20% and 89%, respectively; P=0.02). Baseline symptom severity did not differentiate treatment response in the luteal dosing group (P=0.36). The mean number of days on active medication was 13.5 days in the luteal dosing group and 6.0 days in the symptom-onset group (P<0.001). The mean (SD) dose in the third treatment cycle was 15.2 (+/-5.1) mg/day. Escitalopram was well-tolerated, and adverse events were generally transient. Only one subject discontinued due to adverse events (shoulder pain), but more women reported adverse events in the symptom onset group (79%) than in the luteal dosing group (46%) (P=0.07).

Conclusions: Escitalopram significantly reduced PMDD symptoms with either luteal or symptom-onset dosing. Women with more severe premenstrual symptoms may respond better to luteal dosing than to symptom-onset dosing. Further study is needed to confirm or refute these preliminary data.

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POSTER NO. 257

PILOT EVALUATION OF ATOMOXETINE AUGMENTATION OF CLOZAPINE AS A TREATMENT FOR THE COGNITIVE SYMPTOMS OF SCHIZOPHRENIA

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Objective/Background: Much of the disability associated with schizophrenia has been attributed to the negative aspects of the disease including decreased cognitive abilities. There is preclinical evidence that selective norepinephrine reuptake blockers (NRI) enhance dopamine release and cognitive function. This study evaluated augmentation of clozapine with the novel NRI atomoxetine (Atx) in a series of stable, chronic schizophrenic patients who continued to show deficits related to their illness.

Methods: A sample of ten patients on stable dose clozapine treatment participated in this study. They were given Atx 18 mg/day for 1 week and then 40mg/day for the next three weeks. Symptoms, as assessed by the Positive and Negative Syndrome Scale (PANSS), and daily functioning assessed with the NOSIE, were evaluated weekly. Baseline and endpoint clozapine levels, safety labs, and cognitive battery (including information, orientation, digits forward and backward, finger tapping, categories, digit symbol substitution, and trails A and B) were also conducted. Extrapyramidal symptoms (EPS) were assessed with the Abnormal Involuntary Movement Scale (AIMS), Simpson Angus Scale (SAS), and the Barnes Akathesia Scale (BAS).

Results: In cognitive tests, addition of Atx revealed a trend toward significance for the Trails B Errors item. Among the efficacy measures, NOSIE curiosity item ($F(2,26) = 3.78$, $p = .04$) was significantly different in outcome comparisons by means of ANOVA. Also, a trend toward significance was observed in the PANSS Preoccupation item and several additional items from the NOSIE. Finally, post hoc analyses revealed several additional items from the PANSS and NOSIE that reflected trends toward significance. In EPS items, there was a decrease in the SAS salivation item ($F(4,43) = 2.84$, $p = .04$), improving clozapine-induced hypersalivation. There were no other significant safety findings.

Conclusion: Despite being a small, short-term pilot study, the results indicate possible efficacy for atomoxetine as an adjunctive treatment in schizophrenia and is considered sufficiently positive to suggest further evaluation of improvements in cognitive and social functioning in a future study with adequate power and duration to obtain reliable results.

Source(s) of Funding: The Neuroscience Clinical Research Unit and LaRue D. Carter Hospital at the Indiana University School of Medicine funded this study internally.

POSTER NO. 258

IMMEDIATE VERSUS CONTROLLED RELEASE PAROXETINE: PK PROFILES AT STEADY STATE AND IMPACT OF CYP2D6 METABOLIZER STATUS

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Objective/Background: To compare the steady state (SS) pharmacokinetic (PK) profile of immediate release (IR) paroxetine HCl (PAR) tablets to the SS PK profile of controlled release (CR) PAR tablets, and to also assess the impact of CYP2D6 metabolizer status on both formulations.

Methods: The SS PK profiles of a 20 mg PAR IR tablet, a 25 mg PAR CR tablet, a 40 mg PAR IR tablet, and an investigational 50 mg PAR CR tablet were examined in a series of three independent studies in healthy volunteers. In each study, PAR (IR and/or CR) was administered once daily for 14 days (fasted-state) with a full PK analysis conducted on blood samples drawn on day 14. IR PAR and CR PAR (40mg vs 50mg, respectively) were compared head-to-head (crossover fashion) in one study, with the IR 20mg tablet and the CR 25mg tablet evaluated in separate studies. The IR vs CR head-to-head study included 18 subjects who were extensive metabolizers (EM) and 5 subjects who were poor metabolizers (PM) for CYP2D6.

Results: PAR IR and PAR CR tablets exhibited different SS PK profiles. Whereas overall bioavailability (AUC) was comparable, Tmax was delayed approx 5 hours for CR vs IR. There were also differences in mean Cmin or mean Cmax, which resulted in a smaller degree of fluctuation (DF) between peak and trough values for PAR CR vs IR [DF=(Cmax - Cmin)/(AUC/24)]. For both formulations, the PM subjects were not differentiated from the EM subjects with regard to SS Cmax or AUC values.

Conclusion: These data confirm that paroxetine CR exhibits a later Tmax and smaller DF, both desirable characteristics for a controlled-release vs immediate release formulation. This PK profile may contribute to the improved tolerability reported for paroxetine CR. The lack of phenotype-dependency indicates that paroxetine CR can be prescribed without regard to CYP2D6 status.

Source(s) of Funding: This study was funded by GlaxoSmithKline

POSTER NO. 259

IMPACT OF RISPERIDONE TABLET-SPLITTING ON CLINICAL OUTCOMES AND MEDICATION ADHERENCE

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Background: Tablet-splitting is an increasingly common strategy aimed at reducing the cost of prescriptions paid by healthcare systems, patients, and others. Per-tablet costs often are similar across different dosages. Patients with psychosis may have difficulty understanding and following tablet-splitting instructions. Few data are available describing the clinical impact of tablet-splitting. We examined whether management-initiated risperidone tablet-splitting was associated with changes in medication adherence or service utilization.

Methods: We analyzed retrospective administrative data from veterans prescribed risperidone for schizophrenia or schizoaffective disorder (N=226) during January 2001- March 2003. We report descriptive data for 2 groups: those prescribed tablet-splitting (N=101; "splitters"), and those not prescribed splitting (N=125; "non-splitters"). Outcome measures include means over time for 1) adherence to antipsychotic medications measured by medication possession ratio (MPR, number of days covered by dispensed medication/ total number of days in time period), 2) adherence to outpatient treatment: kept appointment rate (KAR - proportion of scheduled appointments that were kept) and unscheduled:kept appointment ratio (UKR- ratio of unscheduled walk-ins to kept appointments), and 3) clinical outcomes (rate of inpatient admissions as proxy for relapse). We used t-tests for normally distributed data and Wilcoxon tests for non-normal data to compare whether splitters prior to initiating splitting differed from non-splitters and to compare splitters before vs. during splitting.

Results: Prior to initiating splitting, splitters had significantly better adherence, more kept appointments and fewer

	Non-splitters Mean(SD)	**Splitters-prior Mean(SD)**
MPR	0.68(0.34)	0.82(0.41)**
KAR	0.77(0.17)	0.83(0.18)*
UKR	0.12(0.34)	0.06(0.18)**
Mean daily risperidone dose (mg)	3.71(1.92)	3.34(1.73)
Psychiatric admission rate	0.52(1.08)	0.43(1.34)

unscheduled visits than non-splitters.
* $p<0.05$
** $p<0.01$

Splitters had significantly higher MPRs and more unscheduled visits during splitting compared to time prior to splitting, but no significant change in psychiatric admissions.

	Splitters-prior	**Splitters-during**
MPR	0.82(0.41)	1.04(0.56) *
KAR	0.83(0.18)	0.83(0.18)
UKR	0.06(0.18)	0.24(0.47)**
Mean daily risperidone dose (mg)	3.34(1.73)	2.97(1.72)
Psychiatric admission rate	0.43(1.34)	0.37(0.99)

* $p< 0.05$
** $p< 0.01$

Conclusions: Prior to initiating splitting, patients prescribed risperidone tablet-splitting appear to be clinically more stable than non-splitters. After initiating splitting, MPRs for splitters increased. Although higher MPRs generally reflect better adherence, MPRs exceeding 1.0 indicate that patients acquired more medications than needed. During splitting, splitters may have been confused about dose (e.g. taking whole tablets instead of the one-half prescribed) or discarded crumbled tablets, which might explain the increase in unscheduled to kept appointment ratio during splitting. Psychiatric admission rates did not increase during splitting.

Disclosure / Source of Funding: The study was funded by the Mental Illness Research, Education and Clinical Center in Veterans Integrated Service Network 3 and by the Targeted Research Enhancement Program at the Bronx VA Medical Center.

POSTER NO. 260

MULTIPLE RATERS IN CLINICAL TRIALS: A BETTER RESEARCH DESIGN?

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Background: Current research protocols in psychiatric clinical trials frequently specify that subjects be evaluated by the same clinician at every study visit whenever possible. This practice should reduce repeated-measures variance and enhance discrimination between active drug and placebo. Empirical findings concerning this practice are scant and Glaudin, et al (1994) found drug-placebo discrimination was significantly better with multiple raters (MR). Possible explanations for this unexpected finding include interference with establishment of a therapeutic alliance thereby reducing placebo response, reduction of rater biases (positive or negative halo effects where raters see subjects as unchanged in spite of actual change) and providing a type of peer supervision that encourages adherence to rating conventions.

Method: 748 adult outpatients, mostly Caucasian, 30-50 years old and approximately 60% female, completed clinical trials in 12 different studies (Major Depression 7 studies; GAD 2; Social Anxiety Disorder 2; OCD 1) at 3 sites of a research network. SR subjects (n = 453, 61%) were examined by the same clinician and MR subjects (n = 297, 39%) were evaluated by 2 or more clinicians. Every subject had equal probability of study condition and clinicians were unaware of experimental design. Responders improved by at least 50% on the primary efficacy scale (Hamilton Depression Scale, Hamilton Anxiety Scale, Liebowitz Social Anxiety Scale, or Yale-Brown Obsessive-Compulsive Scale); CGI-responders had a final rating of much or very much improved.

Results: MR discrimination between active drug and placebo appeared superior to SR condition in every case but one, where discrimination was equal. Responder rates were twice the placebo rate in two cases. MR was provisionally statistically superior to SR in improvement for comparator as measured by CGI ($G2=5.019$, $df=1$, $p=.025$); other results were nonsignificant.

Conclusion: This study indicates that SR did not reduce variability nor did it increase discrimination between drug and placebo. MR may actually be superior to SR in discriminating between placebo and drug. Results are robust in holding up across positive and negative trials and across therapeutic areas.

Source(s) of Funding: Research was funded entirely by Summit Research Network.

POSTER NO. 261

TOLERANCE TO SOMNOLENCE WITH QUETIAPINE: PRECLINICAL MECHANISMS AND CLINICAL EVIDENCE

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Objective/Background: Somnolence is common in patients taking antipsychotics, but may be transient in patients taking quetiapine because of its receptor binding properties. Quetiapine blocks H1 receptors (responsible for somnolence) at lower doses than D2 receptors (responsible for antipsychotic effects). At doses up to 800 mg/d, the blockade of H1 receptors may contribute to the rapid development of tolerance. The objective was to determine the incidence, severity, and dose-relatedness of somnolence in patients treated with quetiapine.

Methods: Data from 76 trials (12 placebo-controlled) were analyzed retrospectively for reports of somnolence as adverse event, including first onset, severity, and resultant withdrawals.

Results: Among 7894 patients with varying diagnoses treated with quetiapine, 25.5% reported somnolence; 62% resolved by treatment end. Somnolence was mild or moderate in 94.9% of cases; incidence decreased from 15.5% in week 1 to 8.6% in week 6. Only 1.3% of patients withdrew because of somnolence. Somnolence was not dose related.

Conclusion: Results suggest that when daytime somnolence occurs in patients taking quetiapine, rapid tolerance developed by the drug at the H1 receptor produces transient, mild to moderate somnolence that is not dose-related and rarely results in treatment discontinuation.

Source(s) of Funding: AstraZeneca Pharmaceuticals LP

POSTER NO. 262

DOUBLE-BLIND COMPARISON OF ESCITALOPRAM AND PAROXETINE IN THE LONG-TERM TREATMENT OF GENERALIZED ANXIETY DISORDER

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Objective/Background: The purpose of this trial was to compare the efficacy and tolerability of flexible doses of escitalopram with paroxetine in the long-term treatment of GAD. Escitalopram is the most selective SSRI studied to date, and has been shown in three randomized, placebo-controlled, double-blind trials to be effective and well tolerated in treating GAD. There are few studies, however, that compare the efficacy and tolerability of one SSRI to another.

Methods: In this randomized trial, patients with DSM-IV-defined GAD (baseline HAMA >= 18) received one week of single-blind placebo treatment, then 24 weeks of double-blind flexible-dose treatment with either escitalopram (10 - 20 mg/day) or paroxetine (20 - 50 mg/day), followed by a 2-week, double-blind, down-titration period. Mean change from baseline to endpoint (LOCF) in HAMA scores was the primary efficacy variable.

Results: Mean baseline HAMA scores for the escitalopram (N=60) and paroxetine (N=61) groups were 23.7 and 23.4, respectively. Both escitalopram and paroxetine were associated with improvement in anxiety symptoms, with mean changes in HAMA scores from baseline to endpoint of -15.3 and -13.3, respectively (p=0.13). Tolerability measures appeared to favor escitalopram over paroxetine treatment. Significantly fewer escitalopram-treated patients withdrew from the study due to adverse events compared with paroxetine treatment (6.6% vs. 22.6%; p=0.02). Of adverse events reported by >= 20% of patients in either treatment group, diarrhea was reported twice as frequently by escitalopram-treated patients, while ejaculation disorder, anorgasmia and decreased libido were reported at least twice as frequently by paroxetine-treated patients.

Conclusion: These results suggest that escitalopram is as effective as paroxetine in the treatment of GAD, but with a more favorable tolerability profile, and support the use of escitalopram as a first-line treatment.

Source(s) of Funding: Forest Labs

POSTER NO. 263

NORMALIZATION OF COGNITIVE FUNCTION WITH LONG-TERM ZIPRASIDONE OR OLANZAPINE

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Objective: To elucidate the magnitude of improvements in cognitive functioning observed with ziprasidone or olanzapine in a 6-month double-blind continuation study and to determine whether changes resulted in normalization of performance.

Methods: Cognitive tests included verbal learning, executive functioning, visuo-motor speed, and verbal fluency. Standard scores were developed based on age and education-corrected norms (normal performance= z-score =-1.0). "Normalization" was defined as: 1) Performance impaired (z<-1.0) at baseline and unimpaired (z>-1.0) at endpoint and 2) Change in performance =0.5 SD.

Results: Average baseline performance was impaired across all tests. Percentages of patients with impaired performance ranged from 36% (letter fluency) to 89% (WCST perseverative errors). Performance was significantly (p<.01) improved at endpoint in ziprasidone (n=62) and olanzapine (n=71) groups for all variables, with corrected effect sizes of .28 to 1.56. Percentages of patients meeting normalization criteria ranged from 10% (trail making part B) to 37% (word list total learning). For 8/10 variables less than 50% were still impaired. There was no significant between group difference in extent of change and likelihood of normalization.

Conclusions: The typical outcome of continuation treatment with ziprasidone over 6 months was normalization of cognitive performance. Olanzapine treated subjects showed a similar pattern of improvement.

Source of Funding: Supported by funding from Pfizer Inc.

POSTER NO. 264

ARIPIPRAZOLE VERSUS PLACEBO IN PATIENTS WITH AN ACUTE MANIC OR MIXED EPISODE

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Objective: To compare the efficacy and safety of aripiprazole with placebo in patients with Bipolar I disorder experiencing an acute manic or mixed episode.

Methods: This Phase III, multicenter, double-blind, placebo-controlled study randomized 272 acutely manic patients with Bipolar I disorder to aripiprazole 30 mg/day (option to reduce to 15 mg for tolerability) or placebo for 3 weeks. Key outcome measures included the Young Mania Rating Scale (Y-MRS) Total Score, CGI-BP and PANSS Hostility subscale.

Results: Aripiprazole produced significant improvements in the Y-MRS by day 4 and at endpoint compared with placebo (-12.5 vs -7.2, p=0.01). In addition, significantly more patients responded (Y-MRS decrease ≥50%) to aripiprazole vs placebo (53% vs 32%, p=0.01). Aripiprazole also showed significant improvement vs placebo on the CGI-BP Severity of Illness (mania) score and the PANSS Hostility sub-scale score. Aripiprazole and placebo had similar discontinuation rates due to AEs, while aripiprazole had fewer discontinuations due to lack of efficacy than did placebo. There were no significant changes in body weight vs placebo.

Conclusion: This is the second study to demonstrate the efficacy and safety of aripiprazole in the treatment of acute mania in patients with Bipolar I disorder.

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POSTER NO. 265

MULTICENTER STUDY OF THE SAFETY AND EFFICACY OF THE MELATONIN AGONIST LY156735 IN PRIMARY INSOMNIA

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Objective: To present safety and efficacy results of LY156735 in adult human subjects with primary insomnia

Background: While the relationship between melatonin and circadian sleep rhythms is well established, a direct soporific effect of melatonin is controversial. LY156735 is a melatonin agonist with high affinities for mt1 and mt2 melatonin receptors. LY156735 lacks the hypothemic, hypotensive and bradycardic effects of melatonin when administered to humans at doses up to 100 mg.

Methods: This study was a randomized, placebo controlled, double blind crossover study to evaluate the safety and efficacy of LY156735 at doses of 20, 50, and 100 mg in human subjects with primary insomnia. This study was approved by a central IRB. Forty adult subjects received polysomnographic sleep evaluations (PSG) for two consecutive nights for each dose level followed by a 5-day washout between doses. The primary outcome variable was latency to persistent sleep. Subjective evaluations of sleep performance and psychomotor assessments were performed upon awakening the morning after study drug treatment.

Results: Subjects who received 20, 50 or 100 mg of LY156735 experienced statistically significant reductions in sleep latency of 31%, 32% and 41%, respectively, as compared to placebo ($p=0.0003$). No other PSG parameters were affected by LY156735 treatment. LY156735 treatment produced significant reductions in subjective time to fall asleep with 20, 50 and 100 mg producing reductions of 13%, 15% and 16%, respectively, as compared to placebo ($p=0.0050$). No other subjective evaluations of sleep performance were affected by LY156735 treatment. Psychomotor assessments revealed no psychomotor impairment the morning following LY156735 treatment. Adverse events did not differ from placebo in frequency or severity at any dose of LY156735.

Conclusions: Data from this ICH- and CGP-compliant mutlicenter trial indicate that LY156735 at doses up to 100 mg reduce objective PSG and subjective latency to sleep without producing morning-after psychomotor impairment. LY156735 at doses up to 100 mg was safe and well tolerated. Taken together, these results suggest that LY156735 at doses up to 100 mg are safe and efficacious for the treatment of primary insomnia.

Source of Funding: Phase 2 Discovery, Cincinnati, OH, USA and NIH MH66488

POSTER NO. 266

IMPROVEMENT IN GLOBAL FUNCTIONING IN BIPOLAR PATIENTS: RESULTS FROM AN OPEN-LABEL, RISPERIDONE STUDY

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Objective/Background: To examine the effect of risperidone monotherapy on global functioning in patients with bipolar I disorder.

Methods: A 9-week, open-label (OL) extension trial of risperidone was conducted in patients previously randomized to 3 weeks of either placebo or risperidone monotherapy for the treatment of acute mania. The Global Assessment Scale (GAS) was used to assess overall functioning. Changes from OL baseline were analyzed using paired t test.

Results: This study included 105 patients who were previously randomized to placebo (PLA/RIS), and 134 to risperidone (RIS/RIS). Mean age was 35.2, and mean modal dose of risperidone was 4.6 mg. Mean (SD) OL baseline GAS score was 56.1 (17.6) for PLA/RIS patients, and 66.9 (13.0) for RIS/RIS patients. At OL endpoint, mean (SD) scores improved to 66.8 (21.7) and 77.7 (14.7), an improvement of 10.6 and 10.8 points, respectively ($p<.001$ in both). Median scores at OL endpoint were 70.0 and 80.0, respectively. Relative to double-blind baseline, the RIS/RIS group improved by 41.9 points, and the PLA/RIS group by 31.1 points.

Conclusion: Treatment with risperidone resulted in significant and clinically meaningful improvements in overall functioning. Those who received risperidone for the entire 12 weeks improved to a level of minimal or no impairment, while those initially on placebo improved to a mild impairment level, supporting the role of risperidone in helping patients achieve restoration of their functioning.

Source(s) of Funding: Janssen Pharmaceutica Products, L.P.

POSTER NO. 267

MODAFINIL FOR THE TREATMENT OF EXCESSIVE SLEEPINESS ASSOCIATED WITH CHRONIC SHIFT WORK SLEEP DISORDER

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Objective/Background: Shift work sleep disorder (SWSD) is characterized by excessive sleepiness during nighttime work hours and/or insomnia during daytime sleep periods. Modafinil improves wakefulness and enhances performance in narcolepsy and obstructive sleep apnea. The objective of this double-blind study was to evaluate the efficacy and safety of modafinil in patients with excessive sleepiness associated with SWSD.

Methods: This 12-week, randomized, double-blind study enrolled patients who worked ≥5 night shifts/month and had mean sleep latency ≤6 minutes on a screening Multiple Sleep Latency Test (MSLT), a baseline sleep efficiency ≤87.5% on polysomnography, and a diagnosis of SWSD who reported excessive sleepiness for at least 3 months. Patients received either placebo or modafinil 200 mg 60 to 30 minutes before each night shift. At 4-week intervals, patients attended the clinic for simulated night shifts. Efficacy measures included mean sleep latency from nighttime MSLT, patient reported level of sleepiness during night shifts (Karolinska Sleepiness Scale [KSS]), overall clinical condition (Clinical Global Impression of Change [CGI-C]), and impact of sleepiness on sustained attention performance by Psychomotor Vigilance Task (PVT).

Results: Of 209 patients randomized, 153 (73%) completed the study. Modafinil significantly improved objective wakefulness on the MSLT. The change [SD] from baseline in overall mean sleep latency was greater for modafinil (1.7 [3.8]) than for placebo (0.34 [2.8]) (p=.002). Modafinil also improved subjective wakefulness; a significant change [SD] from baseline on the KSS was demonstrated (-1.5 [1.5]) compared with placebo (-0.4 [1.5]) (p<.001). A significantly greater percentage of patients receiving modafinil (74% vs 36%) improved their overall clinical conditions (CGI-C; p<.001) at 12 weeks. Modafinil significantly improved patients' ability to sustain attention. The change [SD] from baseline in the overall mean number of lapses of attention on the PVT was significant for modafinil (-3.8 [21.01]) versus placebo (7.2 [20.8]) (p<.001). The most common adverse events were headache (26% modafinil; 19% placebo) and nausea (9%; 3%). No clinically meaningful differences in clinical laboratory parameters, vital signs, electrocardiographic findings, or physical examinations were demonstrated between the treatment groups.

Conclusion: Modafinil significantly improved wakefulness/alertness in patients with chronic SWSD as measured by objective measures (MSLT) and subjective assessment of sleepiness (KSS), and overall clinical condition (CGI-C). In addition, modafinil was associated with significant improvements in sustained attention. Modafinil was well tolerated. Modafinil may be effective for improving wakefulness in patients with excessive sleepiness associated with shift work sleep disorder.

Source(s) of Funding: Cephalon, Inc., West Chester, PA

POSTER NO. 268

THE BURDEN OF DEPRESSION IN PATIENTS WITH BIPOLAR DISORDER

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Objective/Background: To characterize depressive and manic episodes in a bipolar population in terms of frequency and economic burden to a managed care organization.

Methods: Using claims data (1998-2002) for a bipolar patient sample (ICD-9:296.4-296.8), we characterized episodes of care as depressive or manic based on ICD-9 codes and compared outpatient, pharmacy and inpatient costs using t-tests and multivariate linear regression.

Results: During the study period, 13,119 subjects experienced 14,069 bipolar episodes. Annual outpatient bipolar depression costs were four times as high and inpatient bipolar depression costs were twice as high as those for bipolar mania. Depressive episodes occurred 3 times more frequently (N=3083) as compared to manic episodes (N=1236). The average outpatient, pharmacy and inpatient costs for a depressive episode were $1426, $1721, $1646 compared to $863($p<0.0001$), $1248 ($p<0.0001$), $1736($p=0.54$) for a manic episode. Controlling for age, gender, length of episode, site of index visit and pre-episode costs, the cost of a bipolar depressive episode ($5503) was approximately twice as high as that of mania ($2842).

Conclusion: The economic burden of bipolar depression appears to be greater than that of mania. Preventing or delaying bipolar depression could result in potential cost savings to a managed care organization.

Source(s) of Funding: GlaxoSmithKline, Research Triangle Park, North Carolina

POSTER NO. 269

TRAJECTORY ANALYSIS OF TREATMENT RESPONSE DURING A SIX-MONTH STUDY OF NIGHTLY ESZOPICLONE IN PATIENTS WITH CHRONIC INSOMNIA

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Objective/Background: Data on the long-term efficacy of benzodiazepine receptor agonists for treating insomnia are scarce. Eszopiclone demonstrated statistically significant improvements in mean and median measures of self-reported sleep and daytime function in a six-month double-blind treatment study. The analysis was conducted to determine whether distinct patterns of treatment response could be identified among eszopiclone or placebo-treated patients.

Methods: Patients included 788 men and women 21-69 years of age who reported insomnia (sleep duration $\geq$6.5 hours and/or sleep latency >30 minutes). Eszopiclone 3mg or placebo was taken nightly for six months in this randomized, double-blind study. Weekly self-report sleep data were collected using an interactive voice recording system. Endpoints of sleep latency, total sleep time, and wake after sleep onset were analyzed weekly using the SAS TRAJ procedure to identify different patterns of response. We empirically tested models with 2-5 trajectories per treatment. SAS TRAJ calculates the probability of each subject belonging to each trajectory, and assigns each subject to the most likely trajectory. Linear and quadratic mixture models were tested, using separate models for eszopiclone and placebo groups.

Results: Linear mixture models for the three sleep endpoints in the eszopiclone group were tested. For each endpoint, trajectories of treatment response subgroups had similar slopes, whether we specified 2-5 subgroups, with or without adding a quadratic term. The subgroups differed only in mean symptom levels, but not in their actual time course. Descriptively, each subgroup showed a rapid treatment response followed by a stable course or slight improvement over the subsequent six months. We then tested similar models for the placebo group. The trajectories of treatment response for each sleep endpoint had similar slopes regardless of whether we specified 2-5 groups, or added a quadratic term. The subgroups again differed only in terms of mean symptom level. Descriptively, each placebo subgroup showed a stable course or slight improvement over the six months of treatment.

Conclusion: We did not find distinct treatment response trajectories in insomnia patients treated with eszopiclone or placebo for six consecutive months. These results stand in stark contrast to similar analyses in other disorders, where distinct treatment response profiles are readily identified. The results provide further evidence that six months of nightly eszopiclone treatment is associated with rapid and sustained response and no evidence of tolerance, even among specific patient subgroups.

Source(s) of Funding: Sepracor Inc., Marlborough, MA.; MH24652; AG00972

POSTER NO. 270

FIRST SIX MONTHS OF INPATIENT USE OF ARIPIPRAZOLE AT McLEAN HOSPITAL

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Background: Aripiprazole (Abilify®), the newest atypical antipsychotic, has a unique pharmacological profile. It is a partial-agonist at dopamine D2 and serotonin 5HT1A receptors, and an antagonist at serotonin 5HT2A receptors. Several controlled trails have shown aripiprazole to be effective for both positive and negative symptoms of schizophrenia and schizoaffective disorders, as well as in acute mania, with a very low risk of adverse effects, including weight-gain and extrapyramidal symptoms (EPS). We evaluated the clinical use and tolerability of aripiprazole during its first six months of use at McLean Hospital among inpatients.

Methods: We analyzed medical records of inpatients given aripiprazole between December 2002 and June 2003, for information on diagnosis, presenting symptoms, dosing of aripiprazole and other psychotropics, clinical changes, and adverse effects. Patients were classified by clinician-consensus into major affective and primary psychotic disorder subgroups, based on DSM-IV criteria.

Results: Aripiprazole was given to 142 inpatients (93 women, 49 men) with psychotic major affective, or other disorders. Diagnoses included psychotic disorders (N=54, 38%: 34 schizoaffective, 12 not otherwise specified [NOS], 8 schizophrenia); major affective disorders (N=71, 50%) that included bipolar disorder (N=39: 13 depressed, 13 NOS, 9 mixed, 4 manic), and unipolar major depression (N=32); as well as dementia (N=11) and other miscellaneous conditions (N=6).

Of patients given aripiprazole, 23 (16.2%) were admitted with this agent, and 117 (82.4%) were discharged with it. Mean ± SD total daily doses (mg) were: 13.3 ± 4.7 initially, 17.8 ± 7.0 at maximum, and 16.6 ± 6.3 (or 0.21 ± 0.08 mg/kg) at discharge. Adjusted for weight, there were no significant dosing differences by age or sex, but psychotic patients received 29% higher weight-corrected doses at discharge than were given to major affective disorder patients (0.24 ± 0.10 vs. 0.19 ± 0.07 mg/kg, $p<0.01$).

With aripiprazole treatment, there was an overall increase in the number of psychotropics from admission to discharge, and patients discharged on aripiprazole were 2.6-times more likely to be discharged with at least 2 antipsychotics than those not given aripiprazole at discharge (58.6% vs. 22.7%, $p<0.005$).

There were no significant differences in improvement of CGI and GAF scores by sex or dose of aripiprazole, but CGI scores improved significantly more among major affective disorder than psychotic patients ($p<0.05$). There was no significant difference in GAF scores between the two major diagnostic groups. Adverse effects occurred in 15.5% of patients during aripiprazole treatment, and 3.3-times more often among women than men ($p<0.05$). Most commonly reported adverse effects were agitation, akathisia, insomnia, anxiety, and delirium; weight-gain and EPS were rare (both <0.5%).

Conclusions: Aripiprazole was well tolerated in hospitalized patients with various psychotic, major affective, or other disorders. Further study is required to determine the clinical utility of this well-tolerated antipsychotic in disorders other than schizophrenia.

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POSTER NO. 271

RELAPSE OF DEPRESSION DURING PREGNANCY FOLLOWING DISCONTINUATION OF ANTIDEPRESSANT TREATMENT

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Objective/Background: The current study evaluated the risk for relapse in euthymic women who either discontinued or maintained antidepressant treatment across pregnancy.

Methods: Two hundred and fifty pregnant women with a history of major depression were enrolled in a prospective study with monthly follow up appointments throughout pregnancy using structured clinical instruments. All subjects were euthymic for at least three months prior to and at conception. The group was stratified based on decisions regarding antidepressant treatment from three months prior to conception to 16 weeks gestation: (1) discontinued or lowered antidepressant daily dose for at least one week or (2) maintained antidepressant therapy throughout pregnancy. In this preliminary analysis, we compared the results from the first 103 enrolled study subjects who either discontinued or maintained antidepressant therapy.

Results: Subjects who discontinued antidepressants were 3.6 times more likely to experience relapse of major depression during pregnancy compared to those who maintained antidepressant treatment (95%CI 1.9-6.8).

Conclusion: These preliminary findings suggest that discontinuation of antidepressant during pregnancy is associated with a significant risk for relapse compared to continuation of pharmacotherapy. Results from this prospective study will assist clinicians in assessing the risks and benefits associated with treatment of major depression during pregnancy. Outcome of infants whose mothers either discontinued or maintained antidepressant is currently being analyzed.

Source(s) of Funding: Multi-institutional collaborative RO1 from the National Institute of Mental Health (MH# 56420-05).

POSTER NO. 272

TOLERABILITY AND DISCONTINUATION EFFECTS FOR SERTRALINE VERSUS VENLAFAXINE-XR IN DEPRESSION

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Objective: To compare the safety and tolerability of sertraline vs venlafaxine-XR, including structured assessment of discontinuation symptomatology, based on the Signs & Symptoms of Discontinuation Scale (SSDS).

Method: This was an international, 8-week, double-blind study of outpatients with DSM-IV Major Depressive Disorder (MDD; N=163; 69% female; mean age, 37 years; baseline HAM-D, 23) who were randomised to sertraline (50-150 mg/day; n=79) or venlafaxine-XR (75-225 mg/day; n=84). At the end of 8 weeks of double-blind treatment, subjects tapered off medication at a rate not exceeding 50 mg/day of sertraline and 75 mg/day venlafaxine-XR every 4 days (2-week total taper period). Differences in incidence rates were tested using Fisher's Exact test.

Results: Mean week-8 doses were 105 mg/day for sertraline and 161 mg/day for venlafaxine-XR. A greater proportion of patients discontinued from venlafaxine-XR compared to sertraline (30% versus 16%; p=0.06). During tapering, patients on venlafaxine-XR experienced more discontinuation symptomatology, with a >10% higher incidence of the following SSDS events compared to sertraline: dizziness (44% versus 33%; p=0.22), vivid dreams (42% versus 26%; p=0.069), fatigue (33% versus 22%; p=0.18), and vertigo (17% versus 6%; p=0.052). Time to completion of drug tapering was similar between treatments (median time 4.0 days, both treatments).

Conclusions: Although sertraline and venlafaxine-XR were found to be well-tolerated in the acute treatment of MDD, clear differences in discontinuation effects were found between sertraline and venlafaxine-XR during treatment withdrawal.

Source of Funding: Pfizer Pty Limited.

POSTER NO. 273

A VALIDATION STUDY OF THE SEXUAL INTEREST AND DESIRE INVENTORY (SIDI)

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Objective/Background: The Sexual Interest and Desire Inventory (SIDI) is a clinician-rated instrument for assessing variables associated with womens' sexual desire and sexual interest, as well as changes in sexual desire and interest following pharmacological or psychological treatment. The SIDI is a collaborative effort involving experts in female sexual dysfunction from academic centers and the pharmaceutical industry. We have previously reported on the initial development and preliminary testing of the SIDI (NCDEU 2003, II-21; II-41). Item response analyses of the original 17-item SIDI were used to further refine and improve the instrument. We report here the results of the first validation study using the revised 13-item version of the SIDI.

Methods: The SIDI was administered during a single visit to women with hypoactive sexual desire disorder (HSDD), women with female orgasmic disorder (FOD), and women without a diagnosed sexual disorder (DSM-IV). Subjects also completed the Female Sexual Function Index (FSFI) and an Interactive Voice Response (IVR) version of the Changes in Sexual Functioning Questionnaire (CSFQ) as well as a slightly modified version of the Locke-Wallace Marital Adjustment Scale (MAS) in order to assess general relationship satisfaction.

Results: SIDI scores were significantly different for the three patient groups. Women with HSDD obtained the lowest scores and women without a sexual disorder obtained the highest scores on the SIDI. Additionally, in women with HSDD there was a high correlation between scores on the SIDI and overall scores on the FSFI and the IVR-CSFQ. There was a poor correlation between SIDI scores and scores on the MAS.

Conclusion: The finding that SIDI scores distinguished women with HSDD, FOD and women without a sexual disorder supports the discriminant validity of the SIDI in assessing female sexual desire. The finding that SIDI scores did not correlate with scores on the MAS further supports this conclusion and supports the specificity of the SIDI in assessing sexual desire. Finally, the high correlation of SIDI scores with other measures of sexual dysfunction suggests a high degree of convergent validity for the SIDI. Overall, these results provide strong support for the validity of the SIDI in assessing female sexual interest and desire.

Source(s) of Funding: Boehringer-Ingelheim

POSTER NO. 274

USING A SELF-REPORT DEPRESSION SCALE TO IDENTIFY REMISSION IN DEPRESSED OUTPATIENTS

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Objective/Background: Many depressed patients who have responded to treatment continue to have residual symptoms of depression, and the presence of these residual symptoms is associated with higher rates of relapse and recurrence. Consequently, remission, usually defined as the absence or near absence of symptoms, has been recommended as the primary goal of treatment. It has been suggested that standardized rating scales be used in clinical practice to monitor the course of treatment; however, the time demands of clinical practice make it difficult to use measures such as the Hamilton Rating Scale for Depression (HRSD). The goal of the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project was to derive a cutoff on a self-report depression questionnaire corresponding to the most widely used definition of remission (17-item HRSD score <7).

Methods: Two hundred and sixty-seven depressed outpatients were rated on the HRSD and completed the Clinically Useful Depression Outcome Scale (CUDOS). The CUDOS contains 18 items assessing each of the DSM-IV inclusion criteria for MDD and dysthymic disorder as well as psychosocial impairment and quality of life. The amount of time to complete the CUDOS during a follow-up visit was recorded in 50 patients. All but 2 patients completed the scale in less than 3 minutes (Mean=102.7 seconds; SD=42.7). Studies of the reliability and validity of the CUDOS indicate that the scale has strong psychometric properties. Five hundred and sixty-eight psychiatric outpatients completed the scale and the internal consistency reliability coefficient was .90. Test-retest reliability, examined in 176 patients, was .92. The CUDOS was nearly as highly correlated with the HRSD (r=.69) and the Clinical Global Index of severity (r=.71), clinician ratings of the severity of depressive symptoms, as with the self-rated BDI (r=.81). Thus, the CUDOS is a psychometrically strong instrument that correlates highly with clinician ratings of depression, yet is brief enough to be easily incorporated into clinical practice because on average it takes less than two minutes to complete. We used Receiver Operating Curve analysis to examine the sensitivity, specificity and overall classification rate of the CUDOS for identifying remission on the HRSD.

Results: In the ROC analysis the area under the curve was significant (AUC=.95, p<.001). A high level of agreement was obtained between the self-report and HRSD assessments of remission (kappa=.75).

Conclusion: Self-report questionnaires represent a practical option for thoroughly and objectively evaluating the course of treatment and determining remission status in depressed patients.

Source(s) of Funding: NIMH

POSTER NO. 275

REAL-TIME DIGITAL DATA CAPTURE (DDC): A CLINICAL TRIAL TOOL FOR ENHANCING DATA QUALITY AND PROMOTING CLINICAL RATING RELIABILITY

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Objective/Background: Missing data and inconsistencies across ratings are two of the major problems that interfere with the efficiency and rigor of clinical trials. The problem is especially acute for psychiatric studies where items or totals of different scales assess similar constructs, but congruence of these various measures is never examined during the course of a study. This often leads to inexplicable inconsistencies between supposedly similar measures within given patients, as well as across treatment groups at the end of a trial. The objective of this study is to evaluate the features of an DDC system specifically designed to minimize the aforementioned problems. Novel features of the system include "real-time" data capture which simultaneously employs internal qualitative data checks - features not available with currently marketed systems.

Methods: The DDC system was designed by the authors and employs Palm OS and web-based technology to capture clinical research data in real time. The system replaces electronic case report form (CRF) technologies or eCRF which are remote data entry systems which require the transcription of data from a paper-based source or CRF to the database. With the current system, all data can be collected electronically by the raters and physicians while the subject is present. In the present study, however, the clinical research data were derived from an ongoing clinical trial in Social Anxiety Disorder(SAD). Data were collected in the usual manner (paper CRF), and then were reviewed for completeness and consistency by the pharmaceutical company sponsor. Data were then entered into the DDC system by mock raters to test the automated completeness and consistency checks. All errors identified by the system were logged automatically in the system's audit trail.

Results: At the time of this presentation, data from the first half of the planned 90 patient sample have been entered into the ChiMatrix DDC system. As will be presented in quantitative terms, the system successfully identified a variety of potential errors, including errors of omission and missing values, violations of protocol inclusion and exclusion criteria, violations of rating scale conventions, and inconsistencies between scales (e.g. LSAS and CGI) within and across visits. Following the initial assessment, the sponsor and raters at the study site were provided with post-hoc data queries.

Conclusion: Results to date suggest that if the DDC system were utilized as designed from the inception of the clinical trial, the errors summarized above would have been eliminated. It is important to note that these errors were identified after the CRF had undergone checks by site and sponsor personnel. It is therefore likely that more errors would have been identified had the system been used actively in the study. Additionally, it should be noted that many of these errors now represent irretrievable data points in the study. The mock raters found the interactive alerts, reminders and rating challenges to be unobtrusive and helpful. The system appears cost effective and able to enhance the quality and consistency of clinical data within and across sites. The ultimate goal of this system is the production of clean, high quality data that are available for analysis as soon as the last visit of the last patient is completed.

Source(s) of Funding: Supported by private funding.

POSTER NO. 276

ANTICONVULSANTS IN PREGNANCY AND LACTATION: DIFFERENCES IN ATTITUDES AND PRACTICE PATTERNS AMONG NEUROLOGISTS AND PSYCHIATRISTS

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Introduction: Anticonvulsants are used in the treatment of neurological and psychiatric disorders. While there exist consensus guidelines on the use of anticonvulsants in neurology in childbearing women, there are no uniform consensus guidelines in psychiatry for women who are treated with anticonvulsants for primary affective disorders. The objective of this study was to assess attitudes and practices regarding use of anticonvulsants in childbearing women among neurologists and psychiatrists.

Method: A survey was sent to a random sample of 160 physicians: 40 general psychiatrists, 40 psychiatrists specializing in women's mental health, 40 general neurologists, and 40 neurologists specializing in epileoptogy.

Results: The overall response rate was 42%. Psychiatrists and neurologists were similarly likely to refer their patients for pre-pregnancy consultation, recommend folic acid supplementation, and inform women of childbearing potential of the teratogentic effects of anticonvulsants. However, the specialties differed significantly in attitude and clinical practice in managing pregnant women on anticonvulsants. Overall, neurologists endorsed having a positive to extremely positive attitude toward women planning pregnancy and breastfeeding on anticonvulsants compared to psychiatrists ($p<0.004$). Psychiatrists felt it was extremely important to inform patients of potential risks of "neonatal toxicity" and long-term neurobehavioral effects of in utero exposure to anticonvulsants compared to neurologists ($p<0.006$). With respect to breastfeeding, psychiatrists were more likely than neurologists to discuss as well as recommend specific infant monitoring for potential risks of liver toxicity ($p<0.001$), hematological effects ($p<0.003$), and long term neurobehavioral effects ($p<0.001$) compared to neurologists who rarely recommend specific monitoring for infants exposed to anticonvulsants through breast milk.

Conclusions: Based on their self-reports, psychiatrists and neurologists differed significantly on the management of pregnant women on anticonvulsants. This survey demonstrates the need for evidence-based guidelines for the use of anticonvulsants in women of reproductive age.

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POSTER NO. 277

DIETARY INTAKE PROFILE OF PATIENTS WITH SCHIZOPHRENIA

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Objective/Background: The increasing prevalence of overweight and obesity has become a priority public health issue in the United States. An estimated 64% of U.S. adults are either overweight or obese. Similar trends are observed in patients with schizophrenia. Obesity, a co-morbid condition with schizophrenia, increases the risk of lipid abnormalities, cardiovascular disease, insulin resistance, type II diabetes and certain cancers. We performed a cross-sectional study evaluating the dietary intake of patients with schizophrenia or schizoaffective disorder treated with atypical antipsychotic agents.

Methods: Eighty-eight patients with a diagnosis of schizophrenia or schizoaffective disorder from an urban out-patient clinic participated in this cross-sectional study. The mean age was 41.4 ± 10.1 years. Forty-two (47.7 %) of the patients were receiving olanzapine, 25 (28.4%) clozapine, 15 (17.1%) risperidone and six (6.8%) ziprasidone. Intake was measured using a four day dietary record. To assure accuracy records were reviewed by trained dietary interviewers. Interviewers used neutral probing techniques and food models measuring tools to assure completeness. Estimated intake of individual nutrient totals were calculated by the Minnesota Nutrient Database NDS. Data was compared to age-matched data from the National Health and Nutrition Examination Survey (NHANES), 1999-2000.

Results: The mean body mass index (BMI) for the schizophrenia group was 31.3 kg/m2 (SD=12.7). Mean total daily energy intake in subjects with schizophrenia was 1942 ± 914 kcal, significantly less than the reference group, 2196 ± 1110 kcal (p=0.04). The percentage of calories from carbohydrates, protein, and fat were not statistically significant compared to the age matched NHANES group. While 53% of the subjects had a BMI<30 kg/m2, there was no significant difference in energy intake (1772 ± 792 kcal for BMI > 30 kg/m2 and 1772 ± 792 kcal for BMI< 30 kg/m2). The schizophrenia group commonly ate one to two meals per day which tended to be high in "empty calories". Only four (4.5%) subjects obtained 100% of the daily value for fiber. Intake of sucrose was relatively high (mean= 46 g) indicating a large consumption of cake, cookies, candy and sweetened beverages.

Conclusion: Patients with schizophrenia in this study ate less food than those in the NHANES group yet maintain similar percentages of calorie distribution among macronutrients (carbohydrates, protein, and fat). The finding may suggest that obesity in schizophrenia patients is not solely related to food consumption, but perhaps other effects including medications. Some antipsychotic agents may impair glucose metabolism, induce fatigue and sedation, thereby decreasing energy output. Education and interventions for the schizophrenia population should focus more on overall lifestyle factors such as physical activity and healthy food choices.

Source(s) of Funding: None

POSTER NO. 278

DOUBLE-BLIND COMPARISON OF A FIXED DOSE OF ESCITALOPRAM (10 MG/DAY) AND AN OPTIMAL DOSING REGIMEN OF SERTRALINE (50-200 MG/DAY) IN DEPRESSED PATIENTS

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Objective/Background: This trial was conducted to compare the effectiveness and tolerability of fixed dose escitalopram 10 mg/day and optimally dosed sertraline (50 - 200 mg/day).

Methods: Depressed patients (DSM-IV defined; baseline MADRS >= 22) aged 18-80 years were randomly assigned to 8-weeks of double-blind treatment with escitalopram (10 mg/day) or sertraline (50 - 200 mg/day), following a 1-week single-blind placebo lead-in period. Change from baseline to endpoint in MADRS total score (LOCF) was the primary efficacy measure.

Results: A total of 212 patients received double-blind medication. At the end of trial, the mean sertraline dose was 144 mg/day, and nearly half the sertraline treated patients received 200 mg/day. Completion rates were high (85-86%) for both groups. The mean changes from baseline to endpoint in MADRS scores were -19.1 and -18.4 for the escitalopram and sertraline groups, respectively. At endpoint, 75% and 70% of escitalopram and sertraline treated patients, respectively, were responders (>= 50% improvement from baseline in mean MADRS scores). For patients who were severely depressed at baseline (baseline MADRS >= 30; N=92), mean changes from baseline to endpoint in MADRS scores were -22.4 and -20.4 for the escitalopram and sertraline groups, respectively. Both treatments were well tolerated, with only 2 - 4% of patients discontinuing prematurely due to adverse events.

Conclusion: Fixed dose escitalopram 10 mg/day was comparably effective to sertraline, optimally dosed within the range 50 - 200 mg/day. Both escitalopram and sertraline were generally well tolerated.

Source(s) of Funding: Forest Labs

POSTER NO. 279

THE LONG-TERM IMPACT OF MOOD STABILIZERS ON BODY WEIGHT

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Objective/Background: Despite the availability of effective treatments for bipolar disorder, tolerability issues persist. Medication-related weight changes can negatively impact patient compliance with treatment.
The objective of this study was to assess the long-term effect of lamotrigine on weight in patients with bipolar I disorder.

Methods: Weight data from 588 patients with bipolar I disorder in two long-term maintenance studies of lamotrigine (N=230), lithium (N=167), and placebo (N=191) were assessed. Analyses included observed mean weight change, proportion of patients with ≥7% change in weight and weight-related adverse events (AEs), and a mixed model repeated measures analysis of weight change over time.

Results: Observed mean weight changes were negligible and were similar for subjects receiving lamotrigine and placebo; mean weight for patients on lithium increased over time. The proportion of subjects experiencing clinically important (≥7%) weight changes and weight-related AEs were low and similar between the lamotrigine and placebo treatment groups. A mixed model repeated measures analysis showed that after one year of treatment, patients receiving lamotrigine and placebo had minimal mean weight changes (-1.2kg and +0.2kg, respectively) while patients receiving lithium experienced moderate weight gain (+2.2kg).

Conclusion: Long-term treatment with lamotrigine was not associated with clinically relevant changes in weight in patients with bipolar I disorder.

Source(s) of Funding: Research funded by GlaxoSmithKline

POSTER NO. 280

COMPARATIVE OVERALL EFFECTIVENESS OF SCHIZOPHRENIA PATIENTS TREATED WITH ATYPICAL ANTIPSYCHOTICS OLANZAPINE VERSUS ARIPIPRAZOLE

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Background: Most comparative studies of antipsychotic therapies focus upon efficacy measures only. Assessments which measure combined efficacy, safety, and tolerability (i.e., effectiveness) provide a more comprehensive evaluation of drug performance. We used a new instrument, the Investigator's Assessment Questionnaire (IAQ), to compare patients treated with aripiprazole to those treated with atypical antipsychotics.

Methods: The IAQ was used as a secondary measure in an 8-week, randomized, open-label, multi-center study of atypical antipsychotic treatment in 1268 patients with schizophrenia or schizoaffective disorder. The IAQ is an internally validated, clinician-administered questionnaire with 12 items that evaluate efficacy, safety, and tolerability of antipsychotic therapy. The mean (STDV) total score of the 12 items was compared between the two treatment groups. Lower scores were associated with improved outcomes. As part of the internal validation, mean scores were correlated with an independent measure, time to drug discontinuation (TTD).

Results: In the study, 1,049 patients were treated with aripiprazole, and 219 patients were treated with any of the following atypicals: olanzapine, risperidone, quetiapine, risperidone, ziprasidone, or other. The mean total score for patients treated with aripiprazole was 17.4 ± 8.16 compared to 22.2 ± 8.67 for patients treated with atypicals ($p<.0001$). Mean total score was shown to be correlated with TTD ($r=.493$), and clinical relevance was demonstrated by the observation that a 1 unit increase in the score was correlated with a 10% increase in the hazard for TTD.

Conclusions: Overall effectiveness of antipsychotic therapy was greater for patients treated with aripiprazole versus patients treated with atypical antipsychotics. Choice of therapies among schizophrenics should consider not only efficacy, but also safety and tolerability concerns.

POSTER NO. 281

TREATMENT OF PAIN IN FIBROMYALGIA IS DISTINCT FROM TREATMENT OF MOOD

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Objective/Background: Milnacipran (MIL) is a novel, dual acting reuptake inhibitor that is distinguished from other non-tricyclic agents by its preference for norepinephrine reuptake inhibition over that of serotonin, thus closely mimicking the reuptake properties of amitriptyline. Amitriptyline is used as first-line therapy for many chronic pain disorders, including fibromyalgia syndrome (FMS), a complex widespread pain syndrome. There has been controversy as to whether the therapeutic benefits of re-uptake inhibitor usage in FMS are a result of direct analgesic properties, or via an indirect route through the treatment of mood. We sought to investigate this matter by assessing milnacipran effects upon FMS patients both with and without co-morbid major depression (MDE) at baseline, as determined by the MINI interview.

Methods: A 12-week RCT trial was conducted to evaluate the use of milnacipran in the treatment of patients with FMS. Patient self-report of pain on an electronic diary was supplemented with traditional pain and quality of life inventories during monthly clinic visits. Patients were evaluated for the presence or absence of MDE at the start of the trial using the MINI exam. The patients' mood during the course of the trial was assessed using the Beck Depression Inventory (BDI) at baseline and endpoint.

Results: This 125 patient study, which compared milnacipran 200 mg daily against placebo, demonstrated that milnacipran was statistically effective in reducing pain and fatigue, and improving quality of life, on multiple outcome measures, using both electronic and paper-based data collection methods. Of particular interest is that when patients were stratified based on their MINI diagnosis of MDE, there were clear differences in patient response to therapy. Patients who fulfilled criteria for MDE at baseline had a placebo response rate of 33% (3/9), (where response was defined as a 50% improvement in pain at endpoint) as opposed to a 5% (1/19) placebo response rate in the non-MDE group. In contrast, the treatment response rate (BID dosing) between depressed and non-depressed patients was no different [38% (3/8) and 37% (16/43) respectively].

Conclusion: This study demonstrated that the efficacy of milnacipran was independent of MDE status at baseline, as the treatment response rates were comparable in both groups. In contrast, the placebo response rate appeared to differ between the MDE and non-MDE populations, with the depressed population showing a much higher placebo rate. These data and those from previous controlled trials in FMS suggest that effective treatment of the pain and other symptoms of fibromyalgia is not directly linked to successful treatment of depression, as rates of improvement on pain measures were indistinguishable, regardless of diagnosis of MDE at baseline. However, the placebo response rate was substantially higher in the MDE group, suggesting that the analgesic versus antidepressant effects are distinct. The high placebo effect on a pain endpoint in depressed patients may represent a response characteristic of depressed patients, similar to that noted in trials where improvement in measures of depression are the primary endpoint.

Source(s) of Funding: Supported by Cypress Bioscience, Inc.

POSTER NO. 282

PHARMACOKINETICS OF LAMOTRIGINE AND OXCARBAZEPINE CO-THERAPY

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Objective/Background: In vitro, oxcarbazepine (OXC) and its metabolite 10-monohydroxy (MHD) are weak inducers of UDP-glucuronyl transferase, which may increase lamotrigine (LTG) conjugation.

We investigated the pharmacokinetics (PK) and tolerability of the combination of LTG and OXC in healthy volunteers.

Methods: 47 healthy, non-smoking, adult males were randomized to receive LTG (titrated to 200mg/day) or placebo (PBO) on days 1 - 53. OXC (titrated to 600 mg bd) or PBO were added on days 43 - 53 resulting in 3 parallel cohorts receiving the combinations of LTG+OXC, LTG+PBO or OXC+PBO. PK profiles were obtained at steady state.

Results: AUC(0-24) and Cmax of LTG, OXC and its active metabolite MHD were not significantly affected by cotherapy; all were on average less than 10% lower compared with monotherapy. Adverse events (AEs) were reported more frequently with OXC+LTG than with either monotherapy. The most common AEs headache, dizziness, nausea and somnolence.

Conclusion: Co-administration of LTG and OXC does not affect the PK of either drug. The PK results support co-administration in patients who may benefit from combination therapy.

Source(s) of Funding: Funding provided by GlaxoSmithKline

POSTER NO. 283

UNDERSTANDING AND ADDRESSING REGULATORY QUESTIONS IN THE USE OF TECHNOLOGY SOLUTIONS TO COLLECT PATIENT REPORTED OUTCOMES DATA

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Objective/Background: Patient reported outcomes (PRO) data can be an important component of efficacy evidence in regulatory drug submissions. In some therapy areas these data represent the primary endpoints of pivotal studies. Electronic solutions are acknowledged to address many of the quality and integrity concerns of regulators associated with paper diaries: · The timeliness of diary entry can be measured · Retrospective data entry can be limited · Prospective diary entry can be prohibited · Conflicting and ambiguous data can be eliminated. ePRO data have been submitted successfully to FDA as a component of new drug applications.

Methods: This poster explores remaining regulatory questions, and their solution, that are particular to the use of electronic diaries.

Results: The fundamental difference between paper- and technology-delivered diaries is the involvement and control of the Investigator. Because diary data are defined as source data in the ICH GCP guidelines, and form part of the case history for individual patients, these fall under the responsibility of the investigator. We discuss how an Investigator can be responsible for these data when a technology solution is provided and hosted by the Sponsor or a vendor; and explore a possible definition and responsibility of a "trusted third party". In addition, because diary data are a component of source documentation they should be available for review by the Investigator, and the Investigator should be able to produce these data in the event of a regulatory inspection. We detail how technology solutions facilitate both ongoing review by the Investigator and inspection by an auditor. We also discuss the definition of where the source data resides when using Interactive Voice Response (IVR) systems and handheld devices to collect ePRO data; and what this means in terms of the ability to revisit and review data in the future.

Conclusion: Technology solutions enhance the quality and integrity of patient self-report data. When implemented appropriately, these solutions can also address regulatory questions specific to their use. Both IVR and handheld device solutions represent a significant enhancement to our ability to trust and make decisions based upon data supplied directly from the patient.

Source(s) of Funding: The authors are employees of ClinPhone.

POSTER NO. 284

CORRELATIONS AND FACTOR STRUCTURES WITHIN DATA FROM CONTEMPORANEOUS INTERACTIVE VOICE RESPONSE SYSTEM AND CLINICIAN ADMINISTRATIONS OF THE HAMILTON DEPRESSION RATING SCALE

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Introduction: Interactive Voice Response (IVR) system administration of the Hamilton Depression Rating Scale (HAMD) to patients in clinical trials may have cost and logistical advantages over traditional clinician administration of the HAMD. For a sponsor to use IVR HAMD as the primary efficacy measure in an antidepressant clinical trial, however, the sponsor must be confident that the scores generated by IVR HAMDs are sufficiently similar to those of scores from clinician HAMDs.

Methods: We examined data from 3 multi-center, outpatient, placebo-controlled, antidepressant clinical trials in which both IVR and clinician HAMDs were obtained. We matched IVR HAMDs to clinician HAMDs when the two were obtained from the same patient within 0 to 2 calendar days of each other and when the clinician HAMD was obtained at a study entry visit, a treatment arm assignment visit, or a visit during a double-blind treatment comparison period. We identified for our analyses a total of 3,385 matches from 605 unique patients. Within these matches we examined correlations among the following 38 variables: IVR HAMD 17-item total, IVR HAMD Maier subscale (sum of items 1, 2, 7, 8, 9, and 10), individual IVR HAMD item scores (1 to 17), clinician HAMD 17-item total, clinician HAMD Maier subscale, and individual clinician HAMD item scores (1 to 17). We compared the patterns of correlations among IVR HAMD variables with the corresponding patterns of correlations among clinician HAMD variables, and we subjected the data to factor analysis.

Results: IVR HAMD 17-item total was strongly correlated with clinician HAMD 17-item total (r=0.79), and IVR HAMD Maier subscale was strongly correlated with clinician HAMD Maier subscale (r=0.72). The pattern of item-total correlations in IVR HAMDs was remarkably similar to the pattern of item-total correlations in clinician HAMDs. Correlations between IVR HAMD item scores and corresponding clinician HAMD items scores were 0.64, 0.58, 0.65, 0.70, 0.55, 0.59, 0.60, 0.19, 0.18, 0.53, 0.50, 0.57, 0.50, 0.61, 0.45, 0.35, and 0.00 for items 1 through 17, respectively. Factor analysis of clinician HAMD item data yielded 4 factors that collectively explained 49% of the multifactor variance. A 4-factor solution of the IVR HAMD item data explained 47% of the variance with a remarkably similar structure. HAMD items 1, 2, 3, 7, 8, 10, and 13 loaded >0.4 on the first factor of each of the 4-factor solutions.

Conclusions: IVR administration of the HAMD produces item and total scores that are similar to those from clinician administration of the HAMD. Correlation and factor structures suggest that the information provided by IVR HAMD is not substantively different from that provided by clinician HAMD.

Source of Funding: Eli Lilly and Company

POSTER NO. 285

ATYPICAL ANTIPSYCHOTICS IN THE TREATMENT OF MANIA: A META-ANALYSIS OF RANDOMIZED, PLACEBO-CONTROLLED COMBINATION THERAPY TRIALS

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Introduction: Atypical antipsychotics are frequently used in combination with traditional mood stabilizers in the treatment of bipolar mania. However, the benefits of combination therapy are less well-studied than for monotherapy, and there are no published comparisons of individual atypical antipsychotics. We therefore conducted a systematic review and meta-analysis of randomized, placebo-controlled trials of atypical antipsychotics in combination with traditional mood stabilizers.

Methods: We included primary studies that prospectively compared one of the atypical antipsychotics approved for any indication by the U.S. Food and Drug Administration as of January 2004 (aripiprazole, clozapine, quetiapine, risperidone, ziprasidone, olanzapine) with a placebo control group, in combination with lithium, valproate, or carbamazapine. Studies were identified using Medline search, reviews of meeting proceedings, as well as consultation with study investigators. We attempted to include all studies where results have been analyzed and presented in any forum; thus, there was no requirement that papers be published in a peer-reviewed journal for inclusion. Analyses were performed on the change in Young Mania Rating Scale total score from baseline to endpoint, using last observation carried forward and computing the difference in change scores between each drug and its corresponding placebo arm. A random-effects model with fixed drug effects was used to combine the studies and make comparisons of the drugs to each other and to placebo.

Results: Data from five placebo-controlled combination therapy trials involving a total of 1039 subjects (including 465 placebo-treated subjects) with bipolar mania (pure and/or mixed states) were obtained. One trial of olanzapine reported data after six weeks of treatment, while the other trials reported data after three weeks. Lithium or valproate were used as mood stabilizers in all of the trials, and one trial of risperidone also allowed carbamazepine. All of the drugs demonstrated significant efficacy (i.e., all confidence intervals exclude zero). However, after adjusting for multiple comparisons, pairwise comparisons of individual effects identified no significant differences between drugs.

Conclusion: Olanzapine, risperidone and quetiapine are all superior to placebo in the treatment of bipolar mania when used in combination with a traditional mood stabilizer. Cross-trial comparisons further suggest that differences in efficacy between the drugs, if any, may be small.

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POSTER NO. 286

PLACEBO-LEVEL EPS AND AKATHISIA DURING QUETIAPINE TREATMENT FOR MANIA

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Objective: Examine the incidence of EPS-related adverse events (including akathisia) during treatment with quetiapine for bipolar mania.

Methods: Patients with bipolar I mania treated with quetiapine (up to 800 mg/d as monotherapy or in combination with lithium [0.7-1.0 mEq/L] or divalproex [50-100 mcg/mL]) in placebo-controlled, double-blind studies of up to 12 weeks' duration. Adverse event reports and Simpson Angus Scale (SAS) and Barnes Akathisia Rating Scale (BARS) scores were outcome measures.

Results: EPS-related adverse events (including akathisia) with quetiapine monotherapy (12.9%) were no different than placebo (13.1%). Similarly, EPS-related adverse events with quetiapine plus lithium or divalproex (21.9%) were no different from lithium or divalproex monotherapy (19.2%). The incidence of akathisia was lower with quetiapine monotherapy than placebo (3.3% vs 6.1%), as it was with quetiapine combination therapy compared to lithium or divalproex monotherapy (3.6% vs 4.9%). No significant differences were observed between groups in SAS and BARS scores from baseline to endpoint. Anticholinergic use, a marker for EPS, was low in both groups.

Conclusion: The incidence of EPS and akathisia during quetiapine therapy for bipolar mania is no different from placebo. Avoiding EPS (including akathisia) enhances the tolerability and acceptability of treatment, which is of particular importance for patients with bipolar disorder.

Source(s) of funding: This research was supported by AstraZeneca.

POSTER NO. 287

SAFETY, TOLERABILITY, AND EFFICACY OF PSILOCYBIN IN TREATMENT REFRACTORY OCD

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Objective/Background: Anecdotal reports suggest that the hallucinogen psilocybin helps to relieve symptoms of obsessive-compulsive disorder during and after the acute psychedelic experience. Psilocybin is a potent 5-HT-2A agonist, which resembles the pharmacological mechanism for antiobsessional drug response. The purpose of this study is to: 1. Establish safety and tolerability of psilocybin in human subjects; 2. Collect preliminary data regarding efficacy of psilocybin treatment in OCD; 3. Explore the dose-response relationship; and 4. Explore the relationship between degree of hallucinogenic response and antiobsessional effects.

Methods: Eight subjects (target N=10) with SCID-confirmed OCD and no major comorbid psychiatric disorders received up to 4 different doses of psilocybin in a double-blinded fashion during 4 sessions spaced 1-2 weeks apart. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and a Visual Analog Scale (VAS) for overall symptom severity was administered immediately before ingestion and at 4, 8, and 24 hours post-ingestion. The Hallucinogen Rating Scale (HRS) was administered at 8 hours post-ingestion. Vital signs were monitored.

Results: Eight subjects have been administered a total of 25 doses of psilocybin thus far. No significant adverse effects have been observed and all 25 doses were tolerated well. Five out of eight subjects reported acute improvement in OCD symptoms and at least one subject had long-term (6 months) relief of symptoms lasting beyond the acute psychedelic effects.

Conclusion: Early review of data collected thus far suggests that psilocybin may be safe and well tolerated in subjects with treatment-refractory OCD and may offer at least temporary relief of OCD symptoms.

Source(s) of Funding: The Heffter Research Institute, The Multidisciplinary Association for Psychedelic Studies, and The Nathan Cummings Foundation

POSTER NO. 288

EFFICACY OF QUETIAPINE IN MANIA ASSOCIATED WITH BIPOLAR DISORDER

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Objective: To evaluate the efficacy of quetiapine in the treatment of mania.

Methods: Patients with bipolar I disorder (manic episode, DSM IV) received quetiapine alone (up to 800 mg/day; 12 weeks) or in combination with lithium (0.7-1.0 mEq/L) or divalproex (50-100 mcg/mL) (3 or 6 weeks) in randomized, placebo-controlled, double-blind studies. Efficacy measures included Young Mania Rating Scale (YMRS), response ($\geq$50% decrease in YMRS score), and remission (YMRS$\leq$12) rates.

Results: In a combined analysis of 2 studies, the change from baseline in YMRS score with quetiapine monotherapy was significantly greater than with placebo from Day 4 onward ($p=0.021$), and increased by Day 21 ($p<0.001$) and Day 84 ($p<0.001$). Quetiapine combination therapy also improved YMRS scores within the first week ($p<0.05$) and up to Day 21 ($p=0.014$). Compared to placebo, quetiapine monotherapy or combination therapy resulted in a significantly higher proportion of patients achieving response and remission, and significantly greater improvement in each item of the YMRS and psychotic symptoms at Day 21 and onward.

Conclusions: Quetiapine improves mania as early as Day 4 and offers first-line efficacy for the treatment of a broad range of mood symptoms.

Source(s) of funding: This research was supported by AstraZeneca.

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POSTER NO. 289

RESPONSE TO MOOD STABILIZERS IN OLDER PATIENTS WITH BIPOLAR I DISORDER

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Objective/Background: Efficacy and tolerability of mood stabilizers in older bipolar patients remains understudied. The objective of this research was to examine response to lamotrigine, lithium, and placebo in older bipolar I disorder patients who were enrolled with a current or recent depressed (GW605) or manic/hypomanic/mixed (GW606) mood episode in two recently completed large maintenance studies.

Methods: 588 currently or recently symptomatic bipolar I patients (DSM-IV) were randomized to 18 months of double-blind monotherapy with lamotrigine (100-400mg/day), lithium (0.8-1.1mEq/L) or placebo. Efficacy outcomes (time from randomization until intervention for an emerging manic/hypomanic/mixed or depressive episode) were examined in patients who were age 55 or older at the time of study entry.

Results: The study population included 97 patients meeting age criteria. In this subgroup, time to relapse was significantly prolonged following lamotrigine (median survival = 202 days) but not lithium (139 days) treatment compared with placebo (99 days). The frequency and type of adverse events on lamotrigine treatment were similar when comparing older patients with the general study population.

Conclusion: Lamotrigine may be a useful treatment option for older bipolar patients requiring long-term mood stabilizer treatment due to its favorable efficacy and safety profiles.

Source(s) of Funding: Funding provided by GlaxoSmithKline

POSTER NO. 290

PSYCHOTROPIC UTILIZATION AND CLINICAL PRESENTATION OF HOSPITALIZED VERY-YOUNG CHILDREN

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Objective/Background: Recent studies have reported an increase in the use of psychotropics in preschoolers. Despite this growth in use of psychotropics in preschoolers, little information is available about the clinical characteristics of very young children who receive psychotropics. No information, specific to young children, is available about the prescribing practices of physicians with the most extensive training in child psychopharmacology, i.e. child psychiatrists. Moreover, little safety and efficacy data is available for antidepressants, antipsychotics and mood stabilizers for children under 7 years. The objective of this study was to examine the prevalence and nature of psychotropics prescribed by child psychiatrists to very young children with severe functional impairment secondary to psychiatric pathology and to examine the clinical context in which these psychotropics were prescribed.

Methods: The medical charts of 93 children, who were admitted consecutively to a psychiatric unit and who were less than 7 years old, were retrospectively reviewed.

Results: The children (mean age, 5.4 + 1.1 years) had a high rate of exposure to abuse/trauma (64.5%). Functional impairment as measured on the Clinical Global Assessment (CGAS) scale was high (mean score 14.4+6.7). The majority of the patients were diagnosed with affective disorders (61.3%). Most (78.5%) received psychotropics during the admission. Children were prescribed antipsychotics (50.6%), psychostimulants (41.9%), and antidepressants (36.6%). Of those on psychotropics, the majority (68.5%) were on 2 or more psychotropics. Adverse events were recorded for 12 (12.9%) patients. Eight (8.6%) had neurological side effects such as sedation, insomnia, tremors. Three (3.2%) developed gastrointestinal side effects such as nausea or diarrhea. One (1.1%) developed incontinence.

Conclusions: This naturalistic, retrospective study suggests that psychotropics are commonly prescribed to very young children with extremely severe psychopathology and who are in need of inpatient care. Clinical safety and efficacy trials of these agents in very young children are needed.

Source of Funding: None.

POSTER NO. 291

SERTRALINE AND VENLAFAXINE IN MAJOR DEPRESSION

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Objective/Background: There is significant controversy regarding the relationship between mechanisms of action and the relative effectiveness of antidepressant drugs. This study compared the effects of venlafaxine (VEN)(a mixed serotonin-norepinephrine uptake inhibitor) against sertraline (SER) (a serotonin uptake inhibitor with putative dopamine uptake blocking effects) in major depression.

Methods: 160 outpatients with major depression (Hamilton Rating Scale for Depression [HAM-D]>18) were assigned to double-blind treatment with SER (50-150 mg/day) or VEN (75-225 mg/day) for 8 weeks. Doses of drug were titrated to the maximum if tolerated. The principal outcome measures included the Quality of Life, Enjoyment, and Satisfaction Scale (Q-LES-Q) and the HAM-D.

Results: 122 (76%) completed 8 weeks of treatment, with no differences in percentage of completers between groups (Chi2 p=NS). About 50% of each group achieved the maximum dose. There were no significant differences between groups with regard to overall outcome on any measure (completer or LOCF) or frequency of side effects. Response (>50% reduction in HAM-D) and remission (endpoint HAM-D <8) for the total sample were 52% and 35% (SER) vs. 61% and 47% (VEN) respectively (Chi2 p=NS). Of patients who achieved and maintained the maximum dose of medication for at least 3 weeks, response/remission rates were 64.3% and 52.4% (SER) vs. 73.2% and 53.6%.(VEN) (Chi2 p=NS). There were no differences on the Q-LES-Q. However, in the subset of responders and remitters, SER produced significantly greater improvement.

Conclusion: The effectiveness of SER and VEN did not differ significantly. However, dose and duration of treatment had a major effect on response and remission rates, especially for SER. Therefore, dose and duration of treatment should be considered with future response and remission rate analyses.

Source(s) of Funding: Pfizer, Inc.

POSTER NO. 292

THE EFFICACY OF QUETIAPINE IN THE TREATMENT OF DELUSIONAL DISORDER

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Background: Delusional disorder is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as the presence of at least 1 non-bizarre delusion without accompanying psychopathology, for at least 1 month. Clinical management includes psychotherapy and pharmacotherapy. Literature on the treatment of delusions in other psychotic disorders indicates that antipsychotic drugs may be a viable treatment option. To determine the efficacy of the atypical antipsychotic quetiapine in the treatment of delusional disorder, a separate analysis was conducted on a subset of patients who had participated in the Quetiapine Experience With Safety and Tolerability (QUEST) study, which was a randomized, 4-month, open-label comparison of quetiapine and risperidone in 728 outpatients with a variety of psychotic conditions, including delusional disorder.

Methods: From the QUEST study population, patients who met DSM-IV criteria for delusional disorder were identified. The primary rating instrument was the Positive and Negative Syndrome Scale (PANSS). The efficacy of treatment with quetiapine was assessed as changes from baseline on the PANSS total score and PANSS subscores for the positive scale, the negative scale, and the delusions item. The statistical significance of treatment-related changes in these scores was analyzed using a 2-tailed t-test.

Results: Twelve patients with delusional disorder were identified, 10 of whom were treated with quetiapine: 8 men and 2 women (mean age, 46.3 years; mean duration of treatment, 94.7 days; mean dosage, 254 mg/d). Because only 2 patients with delusional disorder received risperidone, no statistical analysis was possible and no results for risperidone were reported. From the group of 10 quetiapine-treated patients, 2 were excluded from the analysis because they did not meet illness severity or dosing criteria. The remaining 8 patients showed statistically significant decreases from baseline on the PANSS total score (19.5, P=0.007), and on the subscores for the positive scale (4.13, P=0.002) and the delusions item (1.38, P=0.028); the mean score on the PANSS negative scale also declined, but the change failed to achieve statistical significance (3.25, P=0.087).

Conclusions: Based on this subanalysis of data from the QUEST study, quetiapine treatment was associated with significant improvements in symptom severity in 8 patients with delusional disorder. Further studies involving larger numbers of patients treated under blinded conditions are needed to confirm the efficacy of quetiapine in the treatment of delusional disorder.

Funding Source: The research presented was supported by AstraZeneca Pharmaceuticals LP.

POSTER NO. 293

RATER EXPERIENCE IN CNS CLINICAL TRIALS

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Objective/Background: Clinicians who rate the primary efficacy rating instruments in CNS clinical trials often have a broad range of previous clinical and research experience. Lack of appropriate experience may adversely affect the accuracy of ratings and the outcome of a study. In this survey, we have analyzed the extent of previous clinical and research experience as well as the specific experience of raters with the chosen rating instruments.

Methods: This survey includes data from 13 qualification programs conducted by PharmaStar that included at least 50 raters, at least 15 clinical trial sites, included a pre-qualification review of experience, and the use of audience response system (ARS) scoring at the investigator meeting. Protocols included schizophrenia studies (4), mood and anxiety disorders (5), and Alzheimer's disease (4). Frequency analyses were performed on the previous clinical and research experience of raters and their previous experience with the primary rating instrument(s) chosen for the protocol. These rating instruments were scales commonly used in clinical trials for these therapeutic areas. For a sub-set of programs, the experience data was correlated with actual ratings performance on videotaped patient interviews that were observed and scored by ARS at the investigator meeting.

Results: 971 potential raters participated in these 13 programs. 242 raters (24.9%) at the investigator meeting had absolutely no previous experience with the selected primary rating instrument. Lack of ratings experience ranged from 10-52% between studies with an average of 14.8% for schizophrenia studies, 19.8% for mood-anxiety disorders, and 39% for dementia studies. The lowest frequency of raters with no previous ratings experience (10%) was noted in 2 programs using U.S. sites exclusively whereas one multinational dementia program had 52% with no experience for the CIBIC plus. In some programs, the inexperienced raters had significantly more scoring deviations than experienced raters on videotaped interviews shown at the investigator meeting.

Conclusion: In this survey, 24.9% of potential raters had no prior experience with the selected primary rating instrument. Training at the investigator meeting may improve the scoring competency and standardization between raters, but it does not substitute for experience. Further, passive observation and scoring of a videotaped interview done by an experienced interviewer does not equate with the ability to actually conduct a research interview. Consequently, some programs offer supplementary interview training workshops for less experienced raters. Rater qualification programs need to focus on both the interviewing skills of potential raters as well as their scoring competence.

Source(s) of Funding: Data comes from PharmaStar vendor contracts for rater qualification programs provided by: Organon, Johnson & Johnson PRD, Solvay, Eisai, Sanofi-Synthelabo, Novartis, and Glaxo SmithKline

POSTER NO. 295

RACIAL DIFFERENCES IN RESPONSE TO ECT: A COMPARISON OF AFRICAN-AMERICAN VERSUS CAUCASIAN POPULATIONS

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Objective/Background: Recent data have demonstrated that racial minorities receive ECT far less often than other groups (Olfson et al. 1998, Prudic et al. 2001). In the CORE Continuation ECT Trial, an ongoing NIMH-funded, randomized multi-center trial to assess the efficacy of continuation ECT versus pharmacotherapy (lithium+nortriptyline) for treatment of major depressive disorder, we evaluated baseline, treatment, and outcome characteristics of African-American and Caucasian patients receiving an acute course of ECT.

Methods: As of 2003, 432 patients had received an index course of ECT in phase I (acute phase) of the study [average age 55.9; 29.6% psychotic; 67.8% female; 6% (25/432) African-American]. In phase I, all patients received ECT 3X/week. HAM-D 24-item ratings were obtained at baseline and after each ECT. Continuous variables were compared for African-Americans versus Caucasians using the pooled t-test; categorical variables were compared using the chi-square test. LOCF was used to assign an end of study value for missing data; for remission (final two HAM-D$\geq$10), dropouts were assigned the worst case outcome of nonremission. Approximately 80% (344/432) of patients completed the acute course, i.e. remitted or received at least 10 ECT.

Results: Among the total sample, the remission rate was 68.3% (295/432); among completers, 85.8% (295/344) remitted. The average HAM-D at baseline for the total sample was 35.1(sd 7.2) with African-Americans having significantly higher levels than Caucasians [38.1(sd 6.6) vs 34.9 (sd 7.2), p=0.029]. African-Americans had significantly higher levels of psychotic depression (36% vs 27.5%, p=0.0001) and lower levels of melancholic features (40.0% vs 61.9%, p=0.030) as assessed by SCID. African-Americans tended to have a younger age at onset of current illness [49.1(sd 15.2) vs 55.4 (sd 17.2) years, p=0.096] and fewer diagnosed previous episodes [1.5 (sd 2.5) vs 2.6 (sd 4.2), p=0.087]. Although not statistically significant, the length of the current episode in African-Americans was more than twice that of Caucasians [1.7 (sd 3.3) vs 0.8 (sd 1.6) years]. Improvement in HAM-D total by study end was marginally higher in African-Americans [28.4 (sd 9.9) vs 24.5 (sd 10.2), p=0.06]. 76% of African-Americans remitted compared to 67.8% of Caucasians (p=0.393). Approximately 21% (85/407) of Caucasians dropped out compared to only 12% (3/25) of African-Americans.

Conclusion: These data are important given the known bias in prescribing of ECT to racial and ethnic minority populations and raise the question as to whether minority patients are referred later in the course of their illness or if cultural issues influence their diagnoses.

Source(s) of Funding: NIMH grant #MH55495

POSTER NO. 297

USE OF GALANTAMINE HBr IN ELECTROCONVULSIVE THERAPY

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Objective/Background: Electroconvulsive therapy (ECT) is an effective treatment for major depressive disorder, although frequently associated with cognitive impairments. The cognitive impairments of ECT include amnesia (retrograde and anterograde) and delirium. These impairments are directly related to ECT treatment and are not a side effect of anesthesia. The cause of ECT-induced cognitive impairment is not known and no interventions are available to treat it. The purpose of this study was to assess the effectiveness of galantamine in the prevention of the cognitive impairments seen during treatment with ECT, as well as its safety and tolerability.

Methods: Eight consecutive ECT patients were given galantamine 4 mg bid throughout the course of their ECT treatments; a second cohort of nine consecutive ECT patients was not given galantamine. Objective measures of cognitive functioning and depression were performed pre and post ECT. Subjective ratings of depression, confusion and side effects were obtained weekly.

Results: The galantamine and non-galantamine groups did not significantly differ in age, gender or admission GAF scores. No significant between group differences were found for side effects and no patient discontinued galantamine due to side effects. There were no severe adverse drug reactions from galantamine. While the two groups did not differ in global cognitive functioning, the patients receiving galantamine performed significantly better on delayed memory ($F [1,17] = 4.36$, $p<.05$) and abstract reasoning similarities ($F[1,17]=5.27$, $p<.01$) at the completion of ECT. The galantamine group also achieved non significantly greater mood improvement than did the non-galantamine group (repeated measure ANOVA, $F [17] = 3.62$, $p =.075$). No significant differences were found for patients' subjective ratings of depression or confusion. No significant between group differences were found for mean seizure duration, energy administered to induce seizures, blood pressure or heart rate.

Conclusion: These preliminary results suggest that galantamine is both safe and well tolerated during ECT. In addition, our data support the hypothesis that galantamine may reduce cognitive impairment during ECT, especially its impact on new learning. Galantamine may also enhance the antidepressant action of ECT. Further studies of galantamine augmentation of ECT are warranted.

Source(s) of Funding: Internal

POSTER NO. 299

THE USE OF TOPIRAMATE IN PATIENTS WITH EPISODES OF AGGRESSIVE OR IMPULSIVE BEHAVIORS: A REPORT OF SIX CASES

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Objective/Background: Antiepileptic agents such as topiramate are often used for psychiatric conditions as an adjunct to antipsychotics, anxiolytics, and other mood stabilizers. We have observed topiramate to be effective in reducing impulsive acts, such as anger and aggression, and decreasing anxiety.

Methods: Patients who were treated for aggressive and impulsive disorders with topiramate were identified by the treating psychiatrist. The frequency, severity, and intensity of subjective and objective irritability, verbal assaults, assault against objects, others or self were collected via retrospective chart review. Treatment response was retrospectively measured using a revised Overt Aggressive Scale (OAS-R) and two factors that measure impulse control and anger from the Positive and Negative Syndrome Scale (PANSS). Ratings were made at the beginning of topiramate treatment, at the point of symptom remission and at the first sign of any reemergence of symptoms.

Results: Six patients were identified who met the above criteria. Common behaviors included explosive temper, physical and verbal assaults, anxiety, and road rage. All patients had a diagnosis of bipolar disorder, and of the six patients, three showed a seasonal component to their mood states which was stabilized with topiramate. The median dose of topiramate was 100 mg/day (range:15-175mg/day). The mean + standard deviation for time to symptom remission and total duration of follow-up was 4.5 $\pm$ 2.8 months and 11 $\pm$ 4.3 months respectively. All but one patient remained on treatment at the time of evaluation.

Conclusion: Both the OAS-R and PANSS revealed a robust reduction in symptoms of impulsivity, aggression and anger following the initiation of topiramate. If symptoms reemerged, they did not appear to be clinically significant and did not reach the level of pre-treatment. A prospective study is warranted to further delineate the role of topiramate in this patient population.

Source(s) of Funding: none

POSTER NO. 301

OXCARBAZEPINE IN PATIENTS WITH IMPULSIVE AGGRESSION

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Objective/Background: Impulsive aggression is a common clinically significant symptom, but there is a paucity of controlled studies evaluating drug treatment. To evaluate oxcarbazepine benefit in patients with impulsive aggression, and whether diagnosis or other baseline characteristics predict response, a double-blind, placebo controlled, parallel group, random assignment study was conducted.

Methods: Patients responding to advertisements had clinically significant impulsive aggression without other psychiatric symptomatology requiring treatment. Neuroleptics, mood stabilizers and anticonvulsants were exclusionary, as were significant medical illness and risk of injuring others. Of 48 patients, 24 per group, nine dropped out due to adverse events, but 45 completed at least 4 weeks on double-blind medication. Treatment was oxcarbazepine or placebo for 10 weeks, at a variable dose, increasing to 1200 mg/day if tolerated, and to 2400 mg/day if aggression persisted. The main outcome measures were: 1) Change in a Global Overt Aggression rating derived from the Overt Aggression Scale - Modified , and 2) Patient Rated Global Improvement. The Brief Psychiatric Rating Scale was a secondary outcome measure.

Results: Results showed consistent evidence of benefit from oxcarbazepine (compared to placebo) on both primary efficiency measures (psychiatrist rating at $p=0.035$; patient rating at $p=0.01$), and most secondary measures. The few screening and baseline differences between the groups did not explain the outcome differences. There were no significant interactions between diagnosis or other baseline characteristics and differential response to oxcarbazepine or placebo.

Conclusion: Oxcarbazepine appears to benefit adults with clinically significant impulsive aggression. Aggressiveness was reduced across the diagnostic spectrum. Study recruitment was not difficult, suggesting that there may be a substantial number of aggressive individuals who might benefit from treatment. Attempts to replicate this study and to evaluate other medications for impulsive aggression are warranted.

Source(s) of Funding: Novartis Pharmaceuticals Corporation

NCDEU 2004 POSTER ABSTRACTS

Poster Number Index

POSTER NO. 1 **A COMMUNITY LINKAGE INTERVENTION TO TRANSITION INDIVIDUALS WITH A CO-OCCURING SUBSTANCE ABUSE AND PSYCHIATRIC DISORDER FROM ACUTE PSYCHIATRY TO OUTPATIENT CARE**
David A. Smelson, VA New Jersey Health Care System, Lyons, New Jersey/VISN 3 MIRECC/ Department of Psychiatry, University of Medicine and Dentistry-Robert Wood Johnson Medical School, Piscataway, New Jersey
Miklos F. Losonczy, Kathy Castles-Fonseca, Bradley Sussner, Phyllis Stewart, Maureen Kaune, Douglas Ziedonis

POSTER NO. 2 **MIDLIFE OUTCOMES OF 100 ADHD BOYS: PREDICTION BY ASPECTS OF TREATMENT WITH METHYLPHENIDATE**
Jan Loney, Department of Pediatrics, University of Iowa
John R. Kramer, Mary Ann Roberts, Mary McIntosh, Heather Rickels, Christopher Richards

POSTER NO. 3 **A CONTROLLED TRIAL OF EXTENDED-RELEASE BUPROPION IN ADULT ADHD**
Daniel F. Connor, University of Massachusetts Medical Center, Worcester, Massachusetts
James J. Hudziak, Timothy E. Wilens, Barbara R. Haight, Joseph P. Horrigan, Kenneth D. Hampton, Nathalie E. Richard, Jack G. Modell

POSTER NO. 4 **SYMPTOM PROFILES OF CHILDREN AND ADOLESCENTS WITH A DIAGNOSIS OF ADHD, BIPOLAR DISORDER, OR A DEPRESSIVE DISORDER**
Melanie E. Hunziker, College of Pharmacy, The University of Texas at Austin, Texas
Texas Department of Mental Health and Mental Retardation (TDMHMR), Austin, Texas
Anthony DeLeon, Nick C. Patel, M. Lynn Crismon, Alan Shafer, Tawny Bettinger

POSTER NO. 5 **CORRELATIONS OF PLASMA DRUG LEVELS AND ADHD RESPONSE IN JUVENILES ON BUPROPION SR**
W. Burleson Daviss, University of Pittsburgh Medical Center and Western Psychiatric Institute and Clinic
James M. Perel, David A. Axelson, George Rudolph, Richard Gilchrist, Sharon Nuss, David A. Brent, Boris Birmaher

POSTER NO. 6 **SAFETY AND EFFECTIVENESS OF OROS MPH AND ATOMOXETINE**
Jason Kemner, McNeil Consumer and Specialty Pharmaceuticals, Ft. Washington, Pennsylvania
H. L. Starr, Patrick E. Ciccone

POSTER NO. 7 **ADHERENCE MEASURES OF PSYCHOSTIMULANTS USED IN THE TREATMENT OF ADHD IN CHILDREN AND ADOLESCENTS**
Robert J. Sanchez, University of Texas at Austin College of Pharmacy, Austin, Texas
M. Lynn Crismon, Jamie C. Barner, James P. Wilson,Tawny Bettinger

POSTER NO. 8 **SAFETY PROFILE OF BUPROPION SR IN CHILDREN: A RETROSPECTIVE CHART REVIEW**
Elias H. Sarkis, Sarkis Family Psychiatry, Gainesville, Florida
Brian A. Marshall, Stephanie A. M. Sarkis

POSTER NO. 9 **MODAFINIL AS THERAPY FOR ADHD IN CHILDREN: AN 8-WEEK, OPEN-LABEL STUDY**
James M. Swanson, University of California, Irvine, California
Joseph Biederman, Samuel W. Boellner, Craig Earl, Frank A. Lopez

POSTER NO. 10 **A COHORT ANALYSIS OF MEASURED GROWTH PARAMETERS IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER RECEIVING MIXED AMPHETAMINE SALTS (MAS XR) FOR 24 MONTHS**
Thomas J. Spencer, Harvard Medical School, Boston, Massachusetts
Stephen V. Faraone, Jill A. Morgan, David A. Mays, M. Alex Michaels, Simon Tulloch

POSTER NO. 11 **ADHD SYMPTOM RESPONSE AND REMISSION AS A FUNCTION OF STIMULANT THERAPY DOSAGE**
George J. Wan, Ph.D, M.P.H., McNeil Consumer and Specialty Pharmaceuticals
Fort Washington, Pennsylvania
Kimberly M. Cooper

POSTER NO. 12 **PHARMACOKINETICS OF AN EXTENDED-RELEASE FORMULATION OF MIXED AMPHETAMINE SALTS (MAS XR) IN ADOLESCENTS WITH ADHD**
Michael Kahn, Cardinal Health
Samuel W. Boellner, Donald M. Eades, William G. Kramer, David A. Mays
Stephanie C. Read, Simon J. Tulloch

POSTER NO. 13 **THE EFFECTS OF GINKGO BILOBA ON MEMORY IN HEALTHY MIDDLE-AGED VOLUNTEERS**
Keith A. Wesnes, Cognitive Drug Research, Ltd., Reading, United Kingdom
James Ferguson, Orlando Petrini

POSTER NO. 14 **AN ACADEMIC SPECIALTY CLINIC-BASED COMPARISON OF NEXT-STEP SWITCHING VERSUS AUGMENTATION STRATEGIES IN OUTPATIENTS WITH MAJOR DEPRESSIVE DISORDER RESISTANT TO A SINGLE ANTIDEPRESSANT TRIAL**
Papakostas, George, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
Timothy J. Petersen, John W. Denninger, Michael A. Posternak, Dan V. Iosifescu,
Albert S. Yeung,, Andrew A. Nierenberg, Maurizio Fava

POSTER NO. 15 **MODAFINIL AS POTENTIAL TREATMENT FOR COCAINE DEPENDENCE**
Hugh Myrick, Medical University of South Carolina (MUSC), Charleston, South Carolina
Robert Malcolm, Lindsay DeVane, Jennifer Donovan, Jurij Z. Mojsiak, Ahmed M. Elkashef,
Robin Taylor, Kathleen Brady

POSTER NO. 16 **COMPARISON OF LONG-ACTING METHYLPHENIDATE FORMULATIONS IN CHILDREN WITH ADHD: POOLED ANALYSIS OF 2 RANDOMIZED, PLACEBO-CONTROLLED STUDIES**
Raul R. Silva, New York University School of Medicine, New York, New York
Matthew Brams, Ann Childress, Frank A. Lopez, Linda Pestreich, Rafael Muniz

POSTER NO. 17 **A PRELIMINARY CONTROLLED TRIAL OF DIVALPROEX IN PTSD**
Mark B. Hamner, Department of Psychiatry, Ralph H. Johnson VA Medical Center and the Medical University of South Carolina
Richard A. Faldowski, Sophie Robert, Helen G. Ulmer, Michael D. Horner

POSTER NO. 18 **EFFICACY OF DEXMETHYLPHENIDATE EXTENDED-RELEASE CAPSULES IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER**
Thomas Spencer, Massachusetts General Hospital Boston, Massachusetts
J. McGough, R. Muniz, L. Pestreich, S. Kim, H Jiang, C. Agoropoulou, M. Etropolski,
and the Adult ADHD Study Group.

POSTER NO. 19 **RISPERIDONE FOR THE TREATMENT OF REFRACTORY PANIC, SOCIAL ANXIETY AND GENERALIZED ANXIETY DISORDERS**
Elizabeth A. Hoge, Massachusetts General Hospital, Department of Psychiatry,
Boston, Massachusetts
Hannah E. Reese, Alicia C. Doyle, Naomi M. Simon, John J. Worthington, Mark H. Pollack

***POSTER NO. 20** **THE IMPACT OF AFFECTIVE SYMPTOMATOLOGY ON THE MULTIMODAL TREATMENT OF PEDIATRIC ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)**
James Waxmonsky, State University of New York at Buffalo
Michael Cummings, Elizabeth Gnagy, Anil Chacko, Frances Arnold, Kathryn Walker,
Jennifer Drake, Allison Garefino, Jessica Robb, William Pelham

POSTER NO. 21 **EFFECTS OF TREATMENT WITH LY354740, LORAZEPAM, OR PLACEBO INPATIENTS WITH A PRIMARY DIAGNOSIS OF GENERALIZED ANXIETY DISORDER**
Louise R. Levine, Eli Lilly and Company, Indianapolis, Indiana
Mary Anne Dellva, Patrick J. Mesters, Jennie G. Jacobson

POSTER NO. 22 **MODAFINIL IMPROVES COCAINE ABSTINENCE IN COCAINE-DEPENDENCE: A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL**
Charles A. Dackis, Treatment Research Center, University of Pennsylvania School of Medicine,
Department of Psychiatry, Philadelphia, Pennsylvania
Kyle M. Kampman, Kevin G. Lynch, Lauren J. Klein, Maya H. McAllister, Helen Pettinati, Charles P. O'Brien

**Indicates New Investigator Awardee*

NCDEU 2004 POSTER ABSTRACTS

Poster Number Index

POSTER NO. 23 **RESPIRATORY AND AUTONOMIC PANIC DISORDER SUBTYPES: CLINICAL CORRELATES AND RESPONSE TO ALPRAZOLAM-XR**
Brian Klee, Pfizer, Inc., New York, New York
Karl Rickels, Charlotte Kremer

POSTER NO. 24 **SUSTAINED REMISSION/EUTHYMIA WITH QUETIAPINE MONOTHERAPY FOR BIPOLAR MANIA**
Terence Ketter, Stanford University, Department of Psychiatry, Stanford, California
Björn Paulsson, Martin Jones

POSTER NO. 25 **PARTIAL REPORTING OF THE CLINICAL GLOBAL IMPRESSION-IMPROVEMENT SCALE IN POSTTRAUMATIC STRESS DISORDER CLINICAL TRIALS: ARE PTSD CGI-IS MIA?**
Neal Kline, VA San Diego Healthcare System and University of California, San Diego

POSTER NO. 26 **ARIPRAZOLE AS AN AUGMENTOR OF SSRIS IN MOOD AND ANXIETY DISORDER PATIENTS**
John Worthington, Massachusetts General Hospital and Harvard Medical School, Boston, MA
Gustavo Kinrys, Maurizio Fava, Christina Dording , Hannah Reese, Mark Pollack

POSTER NO. 27 **RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND TRIAL OF PAROXETINE CONTROLLED RELEASE IN IRRITABLE BOWEL SYNDROME**
Prakash S. Masand, Duke University Medical Center, Durham, North Carolina
Ashwin A. Patkar, Eric Dube, Stan Krulewicz, Sayad Alamy, Marja Evenden, Marilyn Formal, Indira Varia

POSTER NO. 28 **ATYPICAL ANTIPSYCHOTICS IN THE TREATMENT OF MANIA: A META-ANALYSIS OF RANDOMIZED CONTROLLED MONOTHERAPY TRIALS**
Roy H. Perlis, Massachusetts General Hospital and Harvard Medical School, Boston, MA
Jeffrey A. Welge, Robert M.A. Hirschfeld, Paul E. Keck

***POSTER NO. 29** **ZIPRASIDONE FOR TREATMENT-REFRACTORY GENERALIZED ANXIETY DISORDER: AN OPEN-LABEL, FLEXIBLE-DOSE PILOT STUDY**
Steven Snyderman, University of Pennsylvania School of Medicine, Philadelphia, PA
Moira A. Rynn Karl Rickels

POSTER NO. 30 **ADD-ON AND MONOTHERAPY TOPIRAMATE IN CIVILIANS WITH CHRONIC NON-HALLUCINATORY POSTTRAUMATIC STRESS DISORDER: A PROSPECTIVE OPEN-LABEL STUDY**
Jeffrey Berlant, Private Practice, Boise, Idaho

POSTER NO. 31 **TIAGABINE IMPROVES SYMPTOMS OF SOCIAL ANXIETY DISORDER: AN OPEN- LABEL STUDY**
Philip T. Ninan, Mood and Anxiety Disorders Program, Emory University School of Medicine, Atlanta, Georgia
Laszlo A. Papp

POSTER NO. 32 **METHODOLOGICAL CONSIDERATIONS IN A GAD TREATMENT TRIAL**
Olga Brawman-Mintzer, Department of Psychiatry, Medical University of South Carolina, Charleston, SC
Rebecca G. Knapp, Elizabeth Slate, Hai Lin

***POSTER NO. 33** **FACTORS ASSOCIATED WITH MISSED FIRST APPOINTMENTS IN SUBJECTS VOLUNTEERING TO PARTICIPATE IN A CLINICAL TRIAL OF POSTTRAUMATIC STRESS DISORDER**
Sriram Ramaswamy, Creighton University, Omaha, Nebraska/Veterans Affairs Medical Center, Omaha, Nebraska/University of Nebraska Medical Center, Omaha, Nebraska
Melanie Monnahan, James Madison, Sara Wolff, S. Pirzada Sattar, Frederick Petty, Daniel R. Wilson

**Indicates New Investigator Awardee*

POSTER NO. 34 **ESCITALOPRAM IN THE TREATMENT OF MAJOR DEPRESSION WITH COMORBID GAD**
Naresh P. Emmanuel, Carolina Clinical Research Services, Columbia, South Carolina
Carolyn Cosby, Frances Price

POSTER NO. 35 **QUETIAPINE REDUCES PERSISTENT ANXIETY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER**
Steven D. Targum, PharmaStar, Wayne, Pennsylvania
Howard Hassman, Bijan Bastani, Mohammed Bari

POSTER NO. 36 **REAL-TIME IDENTIFICATION OF MISSING DATA IN A FORMS-BASED PROTOCOL MANAGEMENT SYSTEM**
Andrew P. Ho, University of California, Los Angeles, Torrance, California
David Hindman, Michael W. Smith, Keh-Ming Lin

POSTER NO. 37 **ABRUPT DISCONTINUATION OF ALPRAZOLAM IN PANIC PATIENTS: ANXIETY DURING THE NEXT 24 HOURS**
E. H. Uhlenhuth, University of New Mexico, Albuquerque, New Mexico
Vladan Starcevic, Clifford Qualls, Edward J. Antal, William Matuzas, Javaid I. Javaid

POSTER NO. 38 **A DOUBLE-BLIND COMPARISON OF VENLAFAXINE XR, SERTRALINE, AND PLACEBO IN THE TREATMENT OF PTSD**
Jonathan Davidson, Duke University Medical Center, Durham, North Carolina
Alan Lipschitz, Jeff Musgnung

POSTER NO. 39 **ARE ANXIETY DISORDERS UNDERDIAGNOSED AND UNDERTREATED IN ROUTINE PSYCHIATRIC PRACTICE?**
Joshua E. Wilk, American Psychiatric Institute for Research and Education, Arlington, Virginia
Joyce C. West, William E. Narrow, Donald S. Rae, Lisa Countis, Darrel A. Regier

POSTER NO. 40 **IMPROVEMENT IN PATIENT-REPORTED FUNCTIONING IN PATIENTS WITH SOCIAL ANXIETY DISORDER TREATED WITH VENLAFAXINE XR, PAROXETINE, OR PLACEBO**
Nicholas DeMartinis, University of Connecticut, Farmington, Connecticut
Jeff Musgnung, David Baldwin, Rajiv Mallick

POSTER NO. 41 **EFFICACY OF PREGABALIN IN CLINICALLY RELEVANT SUBTYPES OF GAD**
Mark Pollack, Massachusetts General Hospital, Boston, Massachusetts
Cal K. Cohn, Gwen L. Zornberg, Jerri D. Brock, Kathy Tobias

POSTER NO. 42 **PREDICTORS OF RESPONSE TO A PLACEBO-CONTROLLED, DOUBLE-BLIND TRIAL OF PAROXETINE CONTROLLED RELEASE IN FIBROMYALGIA**
Ashwin A Patkar, Thomas Jefferson University, Department of Psychiatry
Prakash S. Masand, Wei Jiang, Stan Krulewicz, Eric Dube, Cynthia Purcell, Casey McMorran, Kathleen Peindl

POSTER NO. 43 **PREGABALIN IN GENERALIZED ANXIETY DISORDER: INFLUENCE OF DEPRESSIVE SYMPTOMS ON ANXIOLYTIC EFFICACY**
Naomi Simon, Massachusetts General Hospital, Boston, Massachusetts
Dan L. Zimbroff, Mark H. Pollack, Gwen L. Zornberg, Kathy Tobias

POSTER NO. 44 **PREGABALIN'S PHARMACOKINETIC PROFILE SHOWS MINIMAL DRUG-DRUG INTERACTIONS**
Howard N. Bockbrader, Pfizer Global Research and Development
David Wesche

POSTER NO. 45 **ATOMOXETINE AUGMENTATION FOR REFRACTORY ANXIETY DISORDERS**
John Worthington, Massachusetts General Hospital and Harvard Medical School, Boston, MA
Naomi Simon, Gustavo Kinrys, Hannah Reese, Maria Melo, Elizabeth Hoge, Mark Pollack

NCDEU 2004 POSTER ABSTRACTS

Poster Number Index

POSTER NO. 46 **SPEED OF ONSET OF PREGABALIN IN GENERALIZED ANXIETY DISORDER**
Nicholas A. DeMartinis, University of Connecticut Health Center, Farmington, Connecticut
Angelo Sambunaris, Madhukar H. Trivedi, Kathy Tobias, Jerri D. Brock, Gwen L. Zornberg

POSTER NO. 47 **FACILITATED EXTINCTION OF SOCIAL FEARS WITH D-CYCLOSERINE**
Susan G. Ball, Indiana University School of Medicine, Indianapolis, Indiana
Andrew W. Goddard, Angela K. Kuhn, Delynda Wall, Susan Smith, Anantha Shekhar

POSTER NO. 48 **TIAGABINE IN GAD PATIENTS WHO WERE PARTIAL RESPONDERS TO SSRI THERAPY: AN OPEN-LABEL STUDY**
Nihalani, Nikhil, SUNY Upstate Medical University, Syracuse, New York
Thomas L. Schwartz, Arif Khan

POSTER NO. 49 **DOUBLE BLIND PLACEBO CONTROLLED STUDY OF GENDER-BASED VARIABILITY IN NEURO-IMMUNOLOGICAL, NEURO-ENDOCRINE MEASURES WITH SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI) TREATMENT OF POSTTRAUMATIC STRESS DISORDER (PTSD)**
Shehzad K. Niazi, University of Oklahoma Health Sciences Centre, Oklahoma City, Oklahoma
Phebe Tucker, Richard Trautman, Amir Butt, Dorothy B. Wyatt, Robin P. Kimball, Jamie Thompson

POSTER NO. 50 **ATYPICAL ANTIPSYCHOTICS AND RECEPTOR BINDING: ENHANCING COGNITION AND MOOD**
Stephen M. Stahl, Neuroscience Education Institute, San Diego, California/Department of Psychiatry, University of California, San Diego, California
Darius K. Shayegan

POSTER NO. 51 **A MOLECULAR-GENETIC APPROACH TO MODELING PSYCHOTROPIC DRUG RESPONSE**
Hans Stassen, Psychiatric University Hospital, Switzerland
N. Dahmen, I. Giegling, P. Nürnberg, D. Rujescu, T. Sander, M.R. Toliat, A. Szegedi

POSTER NO. 52 **DRUG TREATMENT PATTERNS OF BIPOLAR DISORDER AND ASSOCIATED COSTS**
Eric Wu, Analysis Group/Economics, Boston, Massachusetts
Howard Birnbaum, Paul Greenberg, Zhihong Huang, Ronald Kessler, Andrew Parece, Timothy Victor

POSTER NO. 53 **ANTI-ANXIETY EFFECTS ANALYSIS OF QUETIAPINE IN BIPOLAR DEPRESSION**
Wayne Macfadden, AstraZeneca, Wilmington, Delaware
Joseph R. Calabrese, Robin McCoy, Margaret Minkwitz, Ellis Wilson, Jamie Mullen

POSTER NO. 54 **PRELIMINARY RESULTS ON PREGNANCY OUTCOMES IN BIPOLAR WOMEN: DATA FROM THE LAMOTRIGINE PREGNANCY REGISTRY**
Ruby Castilla, Worldwide Epidemiology, GSK, Research Triangle Park, North Carolina
Sanjiv Kumra, Tracy L. Skaer, A. John Rush, Deanna L. Kelly

POSTER NO. 55 **ARIPIPRAZOLE FOR RELAPSE PREVENTION IN A 26-WEEK PLACEBO-CONTROLLED TRIAL IN BIPOLAR DISORDER**
Dan Oren, Bristol-Myers Squibb Company, Wallingford, Connecticut
Ronald Marcus, Raymond Sanchez, William Carson, Robert McQuade, Linda Rollin, Taro Iwamoto, Elyse Stock

POSTER NO. 56 **ZIPRASIDONE IN BIPOLAR MANIA: EFFICACY ACROSS PATIENT SUBGROUPS**
Steven G. Potkin, University of California, Irvine, California
Paul Keck, Earl Giller, Kathleen Ice, Lewis Warrington, Francine S. Mandel

**Indicates New Investigator Awardee*

POSTER NO. 57 **DONEPEZIL IN BIPOLAR DISORDERS WITH COGNITIVE IMPAIRMENT/ DEMENTIA**
R.C. Young, Department of Psychiatry, Weill Medical College of Cornell University, New York-Presbyterian Hospital, Westchester Division, White Plains, New York
V. Latoussakis, J.M. de Asis, X.L. Baran, B. Kalaya, B.S. Meyers

POSTER NO. 58 **INITIAL SYMPTOMS OF MANIC RELAPSE**
Lisa Jaton, Eli Lilly and Company, Indianapolis, Indiana
John Houston, Ilya Lipkovich, Saeed Ahmed, Jonna Ahl, Matthew Rotelli, Robert W. Baker

POSTER NO. 59 **EFFICACY AND SAFETY OF ZIPRASIDONE IN BIPOLAR DISORDER: LONG-TERM DATA**
Lewis Warrington, Pfizer, Inc., New York, New York
Paul E. Keck, Jr., Steven Potkin, Antony Loebel, Earl Giller, Evan Batzar

POSTER NO. 60 **FLUOXETINE MONOTHERAPY OF BIPOLAR TYPE II MAJOR DEPRESSION - LACK OF MANIC INDUCTION**
Justine Shults

POSTER NO. 61 **EARLY WEIGHT GAIN AS A PREDICTOR OF SUBSTANTIAL WEIGHT: RESULTS FROM SEVEN STUDIES OF OLANZAPINE FOR THE TREATMENT OF BIPOLAR DISORDER**
Pat Toalson, Eli Lilly and Company, Indianapolis, Indiana
Ilya Lipkovich, Saeeduddin Ahmed, Jonna Ahl, Thomas Hardy, Diane Haldane, Robert Baker, Mauricio Tohen

POSTER NO. 62 **VARYING THE CRITERIA FOR RESPONSE AND REMISSION IN BIPOLAR DEPRESSION**
Sara A. Corya, Lilly Research Laboratories, Indianapolis, Indiana
Susan D. Briggs, Michael Case, Mauricio Tohen

POSTER NO. 63 **SERUM LEVEL CHANGES ASSOCIATED WITH SWITCHING PSYCHIATRIC PATIENTS FROM A DELAYED-RELEASE TO AN EXTENDED-RELEASE FORMULATION OF DIVALPROEX SODIUM**
Candace J. Wilkinson, UCLA Mood Disorders Research Program, UCLA Neuropsychiatric Institute, Los Angeles, California
Lori A. Altshuler, Janine Roach, Eric Levander, Susan Marusak, Mark Frye, Rosanne State

POSTER NO. 64 **PHENOCHIPPING OF PSYCHOTIC DISORDERS: A NOVEL APPROACH FOR DECONSTRUCTING AND QUANTITATING PSYCHIATRIC PHENOTYPES**
Alexander B. Niculescu, Laboratory of Neurophenomics/Department of Psychiatry, University of California, San Diego/ VA San Diego Healthcare System VISN-22 MIRECC
Len Lulow, Cory Ogden, Dan R. Salomon, Nicholas Schork, Michael Caligiuri, James B. Lohr

POSTER NO. 65 **A LONGITUDINAL 7-YEAR FOLLOW-UP STUDY OF BIPOLAR DISORDER IN A UNIPOLAR COHORT**
Ruby Castilla, GlaxoSmithKline

***POSTER NO. 66** **THE PREVALENCE OF BIPOLAR DISORDER AND COMORBID DISORDERS IN A SAMPLE OF OTTAWA COUNTY JAIL INMATES**
Omar Elhaj, Case Western Reserve University, Cleveland, Ohio/University Hospitals of Cleveland, Cleveland, Ohio
Joseph R. Calabrese

POSTER NO. 67 **TIME IN EUTHYMIA FOR BIPOLAR PATIENTS RECEIVING OLANZAPINE OR LITHIUM MAINTENANCE TREATMENT**
Mauricio Tohen, Lilly Research Laboratories, Indianapolis, Indiana/Harvard Medical School/McLean Hospital, Belmont, MA
Richard C. Risser, Holland C. Detke, Tammy Forrester, Sara A. Corya

**Indicates New Investigator Awardee*

NCDEU 2004 POSTER ABSTRACTS

Poster Number Index

POSTER NO. 68 **A COMPARISON OF THE EFFICACY AND SAFETY OF QUETIAPINE AND DIVALPROEX SODIUM IN THE TREATMENT OF ACUTE MANIA**
David E. Fleck, University of Cincinnati College of Medicine, Cincinnati, Ohio
Eduardo Dunayevich, Shannon E. Knepfle, K. Sagar Kakani, Kimberly B. Corey, Stephen M. Strakowski

POSTER NO. 69 **ASSESSING THE FUNCTIONAL STATUS OF BIPOLAR PATIENTS**
Sheri E. Fehnel, RTI Health Solutions
Timothy Victor, Ranjani Manjunath

POSTER NO. 70 **DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT STUDY OF MEXILETINE FOR MANIA OR HYPOMANIA**
Ayal Schaffer, Mood Disorders Program, Sunnybrook and Women's College Health Sciences Centre/University of Toronto, Toronto, Canada
Anthony Levitt

POSTER NO. 71 **USE OF A NATURALISTIC DATABASE TO STUDY PATIENTS AND OUTCOMES IN BIPOLAR DISORDER WITH AND WITHOUT COMORBID SUBSTANCE USE**
Kenneth Gersing
Connie Moreadith

POSTER NO. 72 **EXTENDED-RELEASE CARBAMAZEPINE FOR THE TREATMENT OF BIPOLAR DISORDER**
Lawrence Ginsberg, Red Oak Psychiatry Associates, Houston, Texas

POSTER NO. 73 **ADJUNCTIVE ZIPRASIDONE IN BIPOLAR MANIA: LONG-TERM DATA**
Richard Weisler, University of North Carolina, Department of Psychiatry, Raleigh, North Carolina
Lewis Warrington, Judith Dunn, Francine S. Mandel

POSTER NO. 74 **QUETIAPINE IN THE TREATMENT OF DEPRESSIVE SYMPTOMS IN BIPOLAR MANIA**
Claudia F. Baldassano, University of Pennsylvania, Philadelphia, Pennsylvania
Björn Paulsson, Martin Brecher

POSTER NO. 75 **DIVALPROEX AS ADJUNCTIVE THERAPY TO ATYPICAL ANTIPSYCHOTIC MEDICATIONS**
Robert L. Horne, University of Nevada School of Medicine, Las Vegas, Nevada
Cedric Cunanan, Michael Schwiers, Deborah Martz

POSTER NO. 76 **RISPERIDONE VERSUS OLANZAPINE AS ADJUNCTIVE THERAPY IN THE TREATMENT OF PATIENTS WITH BIPOLAR DISORDER WHO ARE RECEIVING A PRIMARY THYMOLEPTIC AGENT**
William Petrie, Psychiatric Consultants, Nashville, Tennessee

POSTER NO. 77 **PAROXETINE AND SUICIDALITY IN A HIGH-RISK POPULATION**
Jane N. Kogan, Massachusetts General Hospital/Harvard Medical School, Boston, MA
Mark S. Bauer, Stephen S. Wisniewski, Lauren Marangell, Michael E. Thase, Gary Sachs

POSTER NO. 78 **A PROSPECTIVE OPEN LABEL STUDY OF ZIPRASIDONE AUGMENTATION FOR BIPOLAR I DEPRESSION**

POSTER NO. 79 **COMPARISON OF OLANZAPINE AND LITHIUM TREATMENT GROUPS BASED ON LITHIUM BLOOD LEVELS: A 52-WEEK BIPOLAR RELAPSE PREVENTION STUDY**
Irwin Greenberg, Eli Lilly and Company, Indianapolis, Indiana
Saeed Ahmed, Yuyan Duan, Kristine Healey, Ilya A. Lipkovich, Mauricio F. Tohen

POSTER NO. 80 **RILUZOLE: AN INVESTIGATION OF THE ANTIDEPRESSANT EFFICACY OF AN ANTIGLUTAMATERGIC AGENT WITH NEUROTROPHIC PROPERTIES IN BIPOLAR DEPRESSION**
J.A. Quiroz, Laboratory of Molecular Pathophysiology
C.A. Zarate, J. Singh, K.D. Denicoff, D.S. Charney, H.K. Manji

POSTER NO. 81 **CARNITINE LEVELS IN PSYCHIATRIC PATIENTS TREATED CHRONICALLY WITH VALPROIC ACID**
Francisco A. Moreno, University of Arizona, Tucson, Arizona
Helen Macey

POSTER NO. 82 **DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF QUETIAPINE IN BIPOLAR DEPRESSION**
Wayne Macfadden, AstraZeneca, Wilmington, Delaware
Joseph R. Calabrese, Robin McCoy, Margaret Minkwitz, Ellis Wilson, Jamie Mullen

POSTER NO. 83 **CARE SATISFACTION, HOPE, AND LIFE FUNCTIONING AMONG ADULTS WITH BIPOLAR DISORDER: DATA FROM THE FIRST 1,000 STEP-BD PARTICIPANTS**
Chad D. Morris, University of Colorado Health Sciences Center, Department of Psychiatry, Denver, CO
David J. Miklowitz, Stephen R. Wisniewski, Alexis A. Giese, Marshall R. Thomas, Michael H. Allen

POSTER NO. 84 **PREVIOUS LITHIUM TREATMENT AS A PREDICTOR OF RESPONSE TO SUBSEQUENT MOOD STABILIZER THERAPY**
Guy Goodwin, Oxford University, Oxford, England
Guy Goodwin, Frederick Goodwin, Robert Leadbetter, Gary Evoniuk, Robin White, Walter Paska

***POSTER NO. 85** **CHARACTERISTICS OF PATIENTS TREATED WITH GABAPENTIN REFERRED TO A BIPOLAR SPECIALTY CLINIC**
Michael J. Ostacher, Massachusetts General Hospital Boston, Massachusetts/Harvard Medical School, Boston, MA
Gary S. Sachs, Heather Schloss, Lori Eisner, Andrew A. Nierenberg

POSTER NO. 86 **USING MOOD STATE TO PREDICT POLARITY OF RELAPSE IN BIPOLAR MAINTENANCE STUDIES**
Joseph Calabrese, Case Western University School of Medicine, Cleveland, Ohio
Charles Bowden, Robert Findling, Eduard Vieta

POSTER NO. 87 **AN INTERACTIVE COMPUTER INTERVIEW FOR MANIA TO ENHANCE HUMAN RATER PERFORMANCE**
Noreen A. Reilly Harrington, Concordant Rater Systems, Boston,MA / Massachusetts General Hospital and Harvard Medical School Boston, Massachusetts
Daniel DeBonis, Daniel C. Lewis, Mary Ann Palko, Roy H. Perlis, Andrew C. Leon, Gary S. Sachs

***POSTER NO. 88** **PRAMIPEXOLE FOR BIPOLAR II DEPRESSION**
Jaskaran Singh, National Institute of Mental Health, Bethesda, Maryland
Jorge Quiroz, Jennifer L. Payne, Kirk D. Denicoff, Husseini K. Manji, Dennis S. Charney, Carlos A. Zarate

POSTER NO. 89 **SAFETY AND TOLERABILITY OF QUETIAPINE IN BIPOLAR MANIA**
Caleb Adler, University of Cincinnati College of Medicine, Cincinnati, Ohio
Stephen M. Strakowski, Martin Brecher

POSTER NO. 90 **RELATION OF FUNDING-SOURCE, METHODOLOGICAL QUALITY AND STUDY-OUTCOME IN BIPOLAR DISORDER DRUGS REPORTS**
Federico Soldani, Harvard Medical School, Department of Psychiatry, Boston, Massachusetts/Cambridge Hospital, Cambridge, Massachusets/McLean Division of Massachusetts General Hospital, Belmont, Massachusetts/University of Pisa School of Medicine, Department of Psychiatry, Pisa, Italy
S. Nassir Ghaemi, Ross J. Baldessarini

POSTER NO. 91 **WORK LOSS ASSOCIATED WITH BIPOLAR DISORDER**
Jacqueline Pesa, AstraZeneca, Wilmington, Delaware
Rahul Sasané, Gregory de Lissovoy, Louis Matza, Josephine Mauskopf

**Indicates New Investigator Awardee*

NCDEU 2004 POSTER ABSTRACTS

Poster Number Index

POSTER NO. 92 **AN OPEN LABEL STUDY OF LAMOTRIGINE IN ADOLESCENTS WITH BIPOLAR MOOD DISORDER**
Gia R. Swope, Mountain West Clinical Trials, L.L.C., Boise, Idaho
Scott P. Hoopes, Loretta S. Amy, Joe Laragan, Brian Frasure

POSTER NO. 93 **A PHARMACOKINETIC INTERACTION STUDY OF LAMOTRIGINE AND OLANZAPINE**
John Ascher, GlaxoSmithKline, Research Triangle Park, North Carolina
Jagdev Sidhu, Sarah Job, Jochen Theis

POSTER NO. 94 **LONG-TERM COGNITIVE IMPROVEMENT: ZIPRASIDONE VERSUS OLANZAPINE**
Christopher R. Bowie, Mt. Sinai Medical Center, New York, New York
Philip D. Harvey, Antony Loebel

POSTER NO. 95 **PHENOMENOLOGY OF RAPID CYCLING BIPOLAR DISORDER: DATA FROM THE FIRST 500 PARTICIPANTS IN THE SYSTEMATIC TREATMENT ENHANCEMENT PROGRAM FOR BIPOLAR DISORDER**
Christopher D. Schneck, University of Colorado Health Sciences Center, Denver, CO
David J. Miklowitz, Joseph R. Calabrese, Michael H. Allen, Stephen R. Wisniewski, Sachiko Miyahara, Melvin D. Shelton, Terrence A. Ketter, Joseph F. Goldberg, Charles L. Bowden, Gary S. Sachs

POSTER NO. 96 **ZIPRASIDONE IN PEDIATRIC PATIENTS: EFFICACY AND TOLERABILITY**
Joseph Gonzalez-Heydrich, Psychopharmacology Program, Children's Hospital, Harvard Medical School, Boston, MA
Carlene MacMillan, Tamara Porter Miller, Olivia Hsin, Frances Johnson

POSTER NO. 97 **OLANZAPINE VERSUS RISPERIDONE IN THE TREATMENT OF BIPOLAR I DISORDER: DETERMINANTS OF CHANGE IN SEVERITY OF BIPOLAR ILLNESS RATINGS**
Potts, Alison, Eli Lilly and Company, Nederland, Colorado
Eileen L. Brown, Saeeduddin Ahmed, Leslie M. Schuh, Robert W. Baker

POSTER NO. 98 **PANDAS WITH CATATONIA: RESPONSE WITH LORAZEPAM AND PLASMAPHERESIS**
Josephine Elia, Department of Child and Adolescent Psychiatry, Children's Hospital of Philadelphia; Department of Psychiatry, University of Pennsylvania School of Medicine
Mary Lynn Dell, David F. Friedman, , Robert A. Zimmerman, Naomi Balamuth, Asim Ahmed, Susmita Pati

***POSTER NO. 99** **ARE ANTIDEPRESSANTS ASSOCIATED WITH SWITCHING FROM MAJOR DEPRESSION TO MANIA IN PATIENTS WITH BIPOLAR I DISORDER?**
Christine J. Truman, New York Presbyterian Hospital/Weill Medical College of Cornell University, New York, NY
Andrew C. Leon, David A. Solomon, Martin B. Keller

POSTER NO. 100 **A COMPARISON OF DIVALPROEX, GABAPENTIN AND OXCARBAZEPINE IN AGGRESSIVE YOUTH**
Sergio R. Korndorfer, Psychopharmacology Program at Children's Hospital, Boston, Massachusetts/Harvard Medical School, Boston, MA
Carlene M. MacMillan, Carl A. Fleisher, Enrico Mezzacappa, William Beardslee, Joseph Gonzalez-Heydrich,

POSTER NO. 101 **EXTENDED-RELEASE CARBAMAZEPINE MONOTHERAPY FOR ACUTE MANIA AND MIXED SYMPTOMS ASSOCIATED WITH BIPOLAR DISORDER**
Richard H. Weisler, Duke University, Raleigh, North Carolina/University of North Carolina, Chapel Hill, North Carolina
Paul E. Keck, Jr., Terence A. Ketter, Alan C. Swann, Amir H. Kalali

POSTER NO. 102 **TRENDS IN ANTIPSYCHOTIC PRESCRIBING TO CHILDREN AND ADOLESCENTS: 1996 TO 2001**
M. Lynn Crismon, College of Pharmacy, University of Texas at Austin, TX / Texas Department of Mental Health and Mental Retardation, Austin, Texas
Nick C. Patel, Kimberly Hoagwood, Michael T. Johnsrud, Karen L. Rascati, James P. Wilson

**Indicates New Investigator Awardee*

POSTER NO. 103 **SLEEP AND MOOD IN PATIENTS TREATED FOR BIPOLAR DISORDER: A TIME SERIES APPROACH**
Michael Bauer, Department of Psychiatry and Psychotherapy, Charité - University Medicine Berlin, Campus Charité-Mitte, Germany/Neuropsychiatric Institute and Hospital, Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, CA
Natalie Rasgon, Paul Grof, Tom Bschor, Laszlo Gyulai, Tasha Glenn, Peter C. Whybrow

POSTER NO. 104 **ACUTE WEIGHT GAIN WITH COMBINATION DIVALPROEX SODIUM AND OLANZAPINE IN CHILDREN AND ADOLESCENT INPATIENTS AT A UNIVERSITY HOSPITAL**
Nicholas A. Votolato, Ohio State University, Columbus, Ohio
Karla M Miller, Sreelatha Pulakhandam, Angelita Sanchez

POSTER NO. 105 **RISK OF MOVEMENT DISORDERS IS LOW IN PEDIATRIC PATIENTS TREATED WITH RISPERIDONE**
Cynthia A. Bossie, Janssen Pharmaceutica Products, L.P., Titusville, New Jersey
Gahan Pandina, Young Zhu, Georges Gharabawi

POSTER NO. 106 **EFFICACY OF INDIPLON-MR IN INDUCING AND MAINTAINING SLEEP IN PATIENTS WITH CHRONIC SLEEP MAINTENANCE INSOMNIA**
Martin Scharf, Tri-State Sleep Disorders Center, Cincinnati, Ohio
T. Roth, J.K. Walsh, P. Jochelson, M. Garber

POSTER NO. 107 **RECRUITMENT OUTCOMES IN CHILD AND ADOLESCENT DEPRESSION**
Robert Chaney, CNS Healthcare, West Palm Beach, Florida
Janice Miller, Dan Kearney, Madeleine Stam, Scott West

POSTER NO. 108 **THE SAFETY AND EFFECTIVENESS OF SERTRALINE FOR THE TREATMENT OF NEURASTHENIA**
Henry Chung, Charles B. Wang Community Health Center, New York, NY
Department of Psychiatry, Harvard Medical School Boston, MA
Jian P. Chen, Hongtu Chen, Susan Seto-Yee, Alan Tso

***POSTER NO. 109** **SAFETY AND EFFICACY OF METHYLPHENIDATE FOR PERVASIVE DEVELOPMENTAL DISORDERS: AN OPEN LABEL STUDY**
Adriana Di Martino, Institute for Pediatric Neuroscience, NYU Child Study Center, New York, NY
Alessandro Zuddas

POSTER NO. 110 **AN OPEN-LABEL TRIAL OF ESCITALOPRAM FOR MAJOR DEPRESSION IN HEPATITIS C**
Ondria C. Gleason, University of Oklahoma College of Medicine, Tulsa, Oklahoma
William R. Yates, Michelle A. Philipsen

POSTER NO. 111 **POLYPHARMACY AMONG CHILDREN & ADOLESCENTS TREATED IN ROUTINE PSYCHIATRIC PRACTICE**
Farifteh F. Duffy, American Psychiatric Institute for Research and Education
William E. Narrow, Joyce C. West, Donald S. Rae, Maritza Rubio-Stipec, Paul Sirovatka, Darrel A. Regier

POSTER NO. 112 **DEXTOFISOPAM: A NOVEL HOMOPHTHALAZINE WITH POTENTIAL FOR TREATMENT OF STRESS-RELATED DISORDERS**
Steven M. Leventer, Vela Pharmaceuticals, Inc.
Karen Raudibaugh, John C. Keogh, Robert F. Kucharik, Naidong Ye, Deirdre O'Hara, Stephanie Salts, Kimm Galbraith, Kevin L. Keim

POSTER NO. 113 **TREATMENT-REFRACTORY CHILDHOOD SCHIZOPHRENIA: CHANGES IN GLUCOSE AND LIPID LEVELS ASSOCIATED WITH ATYPICAL ANTIPSYCHOTICS**
Courtney A. De Thomas, The Zucker Hillside Hospital, North Shore-Long Island Jewish Health System, Glen Oaks, NY
Ginny Gerbino-Rosen, Harvey Kranzler, John Kane, Sanjiv Kumra

POSTER NO. 114 **GROUP EDUCATION IN VETERANS WITH HEPATITIS C**
Emily E. Williams, Northwest Hepatitis C Resource Center/2Behavior Health and Clinical Neuroscience Division, Portland VA Medical Center
Ashlee J. Whitehead, Todd A. Harms, David W. Indest, Peter Hauser

**Indicates New Investigator Awardee*

NCDEU 2004 POSTER ABSTRACTS

Poster Number Index

POSTER NO. 115 **A STUDY OF OXCARBAZEPINE IN THE TREATMENT OF DISRUPTIVE BEHAVIORS OF CHILDREN AND ADOLESCENTS**
Robert B. Lehman
Alan M. Jonas, Surya H. Korn

POSTER NO. 116 **EXPLORATION OF THE EFFECT OF SMOKING CESSATION/REDUCTION ON THE POSITIVE, NEGATIVE AND GENERAL PSYCHIATRIC SYMPTOMS OF PATIENTS ON ANTIPSYCHOTIC MEDICATIONS**
David W. Hindman, Research and Education Institute, Torrance, California/ Harbor-UCLA Medical Center, Torrance, California
Michael W. Smith, Keh-Ming Lin, Andrew Ho, James Smith, Steven De Luna

POSTER NO. 117 **EFFICACY OF SERTRALINE IN AN ANXIOUS SUBGROUP OF YOUTHS WITH MAJOR DEPRESSION**
Karen Dineen Wagner, University of Texas Medical Branch, Galveston, Texas
Paul Ambrosini, John Gillespie, Ruoyong Yang

POSTER NO. 118 **SUBJECTIVE VERSUS OBJECTIVE MEASURES OF COMPLIANCE TO A TRANSDERMAL SMOKING CESSATION PROGRAM AMONG PATIENTS ON ANTIPSYCHOTIC MEDICATIONS**
Steven De Luna, Research and Education Institute, Torrance, California/California State University-Dominguez Hills, Carson, California
David W. Hindman, Steven De Luna, Michael Smith, Aishe Leng, Keh-Ming Lin, Andrew Ho

POSTER NO. 119 **A COMPARISON OF RISPERIDONE-INDUCED WEIGHT GAIN ACROSS THE AGE SPAN**
Daniel Safer, Johns Hopkins Medical Institutions, Baltimore, Maryland

POSTER NO. 120 **METHODS FOR EXAMINING RISK OF DIABETES IN PATIENTS TAKING OLANZAPINE COMPARED TO CONVENTIONAL ANTIPSYCHOTIC MEDICATIONS**
Carlos T. Jackson, Connecticut Department of Mental Health and Addiction Services Research Division, Hartford, CT
Susan M. Essock

***POSTER NO. 121** **THE IMPACT OF CLOZAPINE ON AGGRESSIVE BEHAVIOR AMONG CHILDREN AND ADOLESCENTS WITH SCHIZOPHRENIA**
Inika Schvartz, Department of Psychiatry Research, Zucker Hillside Hospital; Long Island Jewish Medical Center-Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY
David Roofeh, Harvey Kranzler, Ginny Gerbino-Rosen, Sanjiv Kumra, Marjorie McMeniman, Courtney DeThomas

POSTER NO. 122 **SAFETY PROFILE OF ARIPIPRAZOLE IN PSYCHOSIS OF ALZHEIMER'S DEMENTIA: POOLED ANALYSIS**
William Carson, Otsuka-Princeton, New Jersey
Christopher Breder, Elyse Stock, Harry Goyvaerts, Taro Iwamoto, Darlene Jody, Richard Wilber

POSTER NO. 123 **RELIABILITY ANALYSIS AND CONSTRUCT VALIDITY OF THE CHANGES IN SEXUAL FUNCTIONING QUESTIONNAIRE (CSFG) SHORT FORM FOR WOMEN AND MEN**
Elizabeth McGarvey, University of Virginia, School of Medicine, Department of Psychiatric Medicine
Adrienne S. Keller, Anita H. Clayton

POSTER NO. 124 **INCIDENCE OF MORTALITY DURING ANTIPSYCHOTIC CLINICAL TRIALS OF ELDERLY PATIENTS WITH DEMENTIA**
Patrizia Cavazzoni, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana
Carrie Young, John Polzer, Joe Jansen, Jared Kerr, Robert Baker

POSTER NO. 125 **BIPOLAR DEPRESSION AND UNIPOLAR DEPRESSION RESPONSE TO TREATMENT IN THE CONTEXT OF COMORBID ALCOHOLISM**
Ihsan M. Salloum, University of Pittsburgh School of Medicine
Jack R. Cornelius, Levent Kirisci, Antoine Douaihy

**Indicates New Investigator Awardee*

POSTER NO. 126 **TC-1734-112 A SELECTIVE NEURONAL NICOTINIC RECEPTOR (NNR) AGONIST IN THE TREATMENT OF COGNITIVE DISORDERS - PHASE 1RESULTS**
Geoffrey C. Dunbar, Targacept, Inc., Winston Salem, NC
Ramana Kuchibhatla

POSTER NO. 127 **SUBSTANCE USE COMORBIDITY IN MAJOR DEPRESSION: STAR*D PRELIMINARY FINDINGS**
Lori B. Davis, VA Medical Center, Tuscaloosa, Alabama
A. John Rush, Sephen R. Wisniewski, Kayla Rice, Michele Jewell, Paul Cassano, Kathy Shores-Wilson, Melanie Biggs, G. K. Balasubramani, Patrick MCGrath, Mustafa M. Husain, Elizabeth St. John

POSTER NO. 128 **ANTIDEPRESSANT EXPOSURE MAY PROTECT AGAINST DECREMENT IN FRONTAL GRAY MATTER VOLUMES IN GERIATRIC DEPRESSION**
Helen Y. Lavretsky, University of California at Los Angeles, Los Angeles, California
Donna Roybal, Michael J. Ostacher, Chad D. Morris, James G. Waxmonsky

POSTER NO. 129 **EXTENDED USE OF NICOTINE REPLACEMENT THERAPY TO ACHIEVE SMOKING CESSATION IN PERSONS WITH SCHIZOPHRENIA**
W. Dale Horst, Via Christi Research, Inc., Wichita, Kansas
Denise Williams, B.J. Kennedy, Steve Werder, Michael Klein

POSTER NO. 130 **GALANTAMINE IN THE TREATMENT OF DEMENTIA IN HISPANIC PATIENTS: AN EFFECTIVENESS MULTICENTER OPEN LABEL STUDY**
Jacobo Mintzer, Department of Psychiatry, Medical University of South Carolina and the Ralph H. Johnson Veterans Administration Medical Center, Charleston, South Carolina
Alma Aparicio-Cabrera, Luis Eduardo Herrera Gomez, Luis Felipe Cortes Coronado

***POSTER NO. 131** **ETHNIC VARIATIONS IN ANTIDEPRESSANT RESPONSE RATE IN SUBJECTS WITH MAJOR DEPRESSION AND CO-OCCURRING ALCOHOL USE DISORDER: THE ROLE OF SEROTONIN TRANSPORTER POLYMORPHISM**
Katherine G. Ruiz-Mellott, Cedars-Sinai Medical Center, Department of Psychiatry
Russell Poland

POSTER NO. 132 **ENHANCED DELAYED RECALL OF PRE-DRUG WORD LIST FOLLOWING ACUTE LORAZEPAM AND TRIHEXYPHENIDYL ADMINISTRATION IN HEALTHY ELDERLY**
Nunzio Pomara, Nathan Kline Institute, Orangeburg, New York
Lisa M. Willoughby, John J. Sidtis, Thomas B. Cooper, David J. Greenblatt

POSTER NO. 133 **SMOKING REDUCTION IMPACT ON CYP1A2 ACTIVITY IN A GROUP OF PATIENTS RECEIVING ANTIPSYCHOTICS**
Michael W. Smith, Harbor-UCLA Medical Center, Department of Psychiatry, Torrance, California/Research and Education Institute, Torrance, California/ UCLA Geffen School of Medicine, Department of Psychiatry, Los Angeles, CA
Keh-Ming Lin, David W. Hindman, Andrew P. Ho, Smith L. James, Aishe Leng

POSTER NO. 134 **MEASUREMENT OF OLFACTORY ABILITY: ODOR IDENTIFICATION IS NOT EQUIVALENT TO OLFACTORY THRESHOLD**
George Trapp, Mental Health Service, Veterans Affairs North Texas Care System, Dallas, TX / University of Texas Southwestern Medical Center
Andrew L. Schmitt, Damekrian L. Gamble

POSTER NO. 135 **LONG-TERM SAFETY AND ADVERSE EVENTS OF RISPERIDONE IN CHILDREN, ADOLESCENTS AND ADULTS WITH MR/DD**
Jessica A. Hellings, University of Kansas Medical Center, Kansas City, Kansas
Alicia Cardona, Jennifer R. Zarcone, Stacey M. Ward, Stephen R. Schroeder

**Indicates New Investigator Awardee*

NCDEU 2004 POSTER ABSTRACTS

Poster Number Index

POSTER NO. 136 **MEMANTINE MONOTHERAPY IS EFFECTIVE AND SAFE FOR THE TREATMENT OF MILD TO MODERATE ALZHEIMER'S DISEASE: A RANDOMIZED CONTROLLED TRIAL**
Nunzio Pomara, New York University School of Medicine, New York, New York
Elaine R. Peskind, Steven G. Potkin, Scott McDonald, Yang Xie, Ivan Gergel

POSTER NO. 137 **MEMANTINE IS SAFE FOR SHORT- AND LONG-TERM TREATMENT OF DEMENTIA**
Stephen M. Graham, Forest Research Institute, Jersey City, New Jersey
Jeffrey M. Jonas, Grace S. Lee, Margaret Ann Goetz, Albrecht Stöffler, Yvonne Wirth

POSTER NO. 138 **THE INFLUENCE OF ETHNIC BACKGROUND AND CARDIOVASCULAR RISK FACTORS ON COGNITIVE ASSESSMENT OF A LONGITUDINAL COMMUNITY BASED SAMPLE**
Jacobo Mintzer, Medical University of South Crolina, Department of Psychiatry, North Charleston, SC
Paul Nietert, David Bachman, Lotta Granholm-Bentley, Mark Kindy, Kumar Samaburti, Narayan Bhat

POSTER NO. 139 **NEUROPROTECTIVE PROPERTIES OF QUETIAPINE: A POSSIBLE MECHANISM IN TREATMENT OF PSYCHOSIS?**
Andrius Baskys, VA Health Care System MIRECC, Long Beach/Department of Psychiatry and Human Behavior, University of California, Irvine, CA
Liwei Fang, Ildar Bayazitov

POSTER NO. 140 **EFFECTS OF GALANTAMINE AND DONEPEZIL ON ATTENTION IN PATIENTS WITH MODERATE-TO-SEVERE ALZHEIMER'S DISEASE**
Keith A Wesnes, Cognitive Drug Research, Ltd., Reading, United Kingdom
Allistair Burns, Michael Gold, Kershaw Paul

POSTER NO. 141 **FUNCTIONAL AND BEHAVIORAL EFFECTS OF MEMANTINE IN ALZHEIMER'S DISEASE**
Jason T. Olin, Forest Research Institute, Jersey City, New Jersey
Jeffrey L. Cummings, Christopher van Dyck, Frederick A. Schmitt, Stephen M. Graham, James Jin, Pierre N. Tariot

POSTER NO. 142 **A DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL OF C-1073 (MIFEPRISTONE) IN THE TREATMENT OF PSYCHOTIC MAJOR DEPRESSION**
Charles DeBattista, Stanford University, Department of Psychiatry and Behavioral Sciences/ Corcept Therapeutics, Inc.
Joseph Belanoff, Gopal Saha, Alan Schatzberg

POSTER NO. 143 **MEMANTINE PREVENTS Aβ_{1-40}-INDUCED APOPTOTIC CELL DEATH IN THE RAT HIPPOCAMPUS**
Pradeep Banerjee, Forest Research Institute, Jersey City, New Jersey
Ian Paul, Valerie Wanzo, Jose Javier Miguel-Hidalgo

POSTER NO. 144 **LET THE HAMILTON RATING SCALE FOR DEPRESSION SPEAK FOR ITSELF**
Leon I. Rosenberg, The Center for Emotional Fitness, Moorestown, New Jersey
Jamie Bella Rosenberg

POSTER NO. 145 **A 26-WEEK, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF DIVALPROEX SODIUM ER AUGMENTATION OF DONEPEZIL FOR COGNITION AND BEHAVIOR IN MILD/MODERATE ALZHEIMER'S DISEASE**
Julie Coleman, University Behavioral Healthcare, University of Medicine and Dentistry of New Jersey
Peter Aupperle, Anjali Patel, Kevin DeMarco, David Foran

POSTER NO. 146 **NATIONAL PATTERNS IN THE CONTINUITY OF ANTIDEPRESSANT TREATMENT FOR DEPRESSION**
Mark Olfson, Columbia University
Steven C. Marcus, George J. Wan, Michael A. Tedeschi

POSTER NO. 147 **CLINICAL COURSE OF CATIE PATIENTS**
M. Saleem Ismail, University of Rochester
Lon S. Schneider, Karen S. Dagerman, Sonia Davis, Pierre Tariot

POSTER NO. 148 **PRE-RANDOMIZATION WORSENING OF INDIVIDUAL SYMPTOMS OF DEPRESSION: DOES INCREASED ANXIETY PRIOR TO TREATMENT PREDICT PLACEBO RESPONSE?**
Kenneth R. Evans, Axon Clinical Research, Toronto, Canada
Glen Wunderlich, Terrence Sills

POSTER NO. 149 **A SURVEY OF CLINICIANS REGARDING THE TREATMENT OF ALZHEIMER'S DISEASE IN 2003**
Rajnish Mago, Thomas Jefferson University, Philadelphia, Pennsylvania
Prakash Masand, Ashwin Patkar, Murali Doraiswamy

POSTER NO. 150 **IM ZIPRASIDONE IN AGITATED PATIENTS WITH BIPOLAR DIAGNOSES**
David G. Daniel, Bioniche Development, Inc., McLean, Virginia
Shlomo Brook, Lewis E. Warrington, Antony Loebel, Stephen Murray

POSTER NO. 151 **RESPONSE TO MEMANTINE TREATMENT BASED ON MULTIPLE DEFINITIONS OF RESPONDERS**
Jason T. Olin, Forest Research Institute, Jersey City, New Jersey
Frederick A. Schmitt, Pierre N. Tariot, Jeffrey L. Cummings, Joanne M. Bell, Wendy Ma

POSTER NO. 152 **HIGH-DOSE ZIPRASIDONE: EFFICACY AND TOLERABILITY IN CLINICAL PRACTICE**
Daniel A. Deutschman, Southwest General Health Center, Middleburg Heights, Ohio
Douglas H. Deutschman

POSTER NO. 153 **AN ITEM RESPONSE THEORY ANALYSIS OF THE HAMILTON DEPRESSION RATING SCALE: GENDER DIFFERENCES IN MEASURING DEPRESSION SEVERITY**
Terrence L. Sills, Axon Clinical Research
Kenneth R. Evans, Nina Engelhardt, Steven C. Gelwicks, David J. DeBrota

POSTER NO. 154 **ASSESSMENT OF SEROTONIN TYPE 1A (5-HT1A) RECEPTOR GENOTYPE IN A NORMAL VERSUS A DEPRESSED POPULATION AND THE RELATIONSHIP TO PREDICTABILITY OF ANTIDEPRESSANT RESPONSIVENESS**
Toya M. Bowles, Organon Pharmaceuticals USA
Gary M. Levin, Taimour Y. Langaee, Jennifer Y. Tan, Hossein N. Yarandi, Julie A. Johnson, William J. Millard

POSTER NO. 155 **NEW SADHART ANALYSIS: POST MI DEPRESSION, A CAUSE OR CONSEQUENCE OF MYOCARDIAL INFARCTION**
A. H. Glassman, Department of Psychiatry, Columbia University, New York, New York
W. Harrison, M. Gaffney, P.A. Shapiro

***POSTER NO. 156** **REDUCED MUSCARINIC CHOLINERGIC2 RECEPTOR BINDING IN BIPOLAR DISORDER USING PET AND [F-18]FP-TZTP**
Dara M. Cannon, National Institue of Mental Health, Bethesda, Maryland
A. Nugent, R.E. Carson, J. Williams, S. Wood, G. Solorio, D. O. Kiesewetter, W. C. Eckelman, W. C. Drevets

POSTER NO. 157 **SEVOFLURANE BURST SUPPRESSION THERAPY FOR TREATMENT-RESISTANT DEPRESSION**
Terrence S. Early
Shana Schreiber, Chuck Holzer

**Indicates New Investigator Awardee*

NCDEU 2004 POSTER ABSTRACTS

Poster Number Index

POSTER NO. 158 **ARE THERE DIFFERENCES BETWEEN DEPRESSED PSYCHIATRIC OUTPATIENTS WHO WOULD AND WOULD NOT QUALIFY FOR AN ANTIDEPRESSANT EFFICACY TRIAL?**
Michael Posternak, Rhode Island Hospital/Brown University School of Medicine, Providence, RI
Mark Zimmerman, Iwona Chelminski

POSTER NO. 159 **RECURRING SYMPTOMS ACROSS CONSECUTIVE EPISODES OF MAJOR DEPRESSION**
Claudia Carmassi, University of Pisa, Pisa, Italy
Ellen Frank, Andrea Fagiolini, John Scott, David J. Kupfer

POSTER NO. 160 **INCREASED RESPONSE TO PHARMACOTHERAPY IN CHILDHOOD MDD WITH FLEXIBLE DOSE AND EXTENDED TREATMENT: A PRELIMINARY REPORT**
Graham J. Emslie, University of Texas Southwestern Medical Center, Dallas, Texas
Carroll W. Hughes, Jennifer Farnum, Jeanne Rintelmann, Jully Kim, Elizabeth Burroughs

POSTER NO. 161 **A REVIEW OF SSRI COMPARISON TRIALS**
Mark Zimmerman, Rhode Island Hospital/Brown University School of Medicine, Providence, RI
Michael Posternak, Iwona Chelminski

POSTER NO. 162 **STEADY-STATE BIOEQUIVALENCE OF ONCE-DAILY AND TWICE DAILY TABLET FORMULATIONS OF BUPROPION HCL**
Okponanabofa Eradiri, Biovail Technologies, Ltd., Chantilly, Virginia
John C. K. Lai, Keith T. Muir, Suryanarayana M. Sista

POSTER NO. 163 **ABSENCE OF SEXUAL DYSFUNCTION IN PATIENTS WITH MDD TREATED WITH GEPIRONE-ER**
Leonard R. Derogatis, Johns Hopkins Center for Sexual Health and Medicine, Baltimore, Maryland
Anita H. Clayton, Neely Ivgy-May, Steven B. Hollander, John H. Simmons, Kimberly Boyle, Michael Gibertini

***POSTER NO. 164** **AGE EFFECT ON CITALOPRAM DISPOSITION DEFINED BY A POPULATION PHARMACOKINETIC ANALYSIS**
Yan Feng, Department of Pharmaceutical Sciences, School of Pharmacy, University of Pittsburgh
Bruce G. Pollock, Steven Roose, Margaret A. Kirshner, Francis E. Lotrich, David J. Kupfer, Robert. R. Bies

POSTER NO. 165 **ESCITALOPRAM IN THE LONG-TERM TREATMENT OF GENERALIZED ANXIETY DISORDER**
Jonathan Davidson, Duke University Medical Center
Anjana Bose, Qin Wang

POSTER NO. 166 **HEPATIC MONITORING IN CLINICAL TRIALS: A CASE STUDY**
Oleg Martynov, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN
J. Raskin, B. Pangallo, C. Stroud, H. A. Read, A. Rosen, D. D'Souza, J. Wernicke

POSTER NO. 167 **CHROMIUM PICOLINATE: ATYPICAL DEPRESSION, CARBOHYDRATE CRAVING AND CLINICAL RESPONSE**
John P. Docherty, Comprehensive Neuroscience, Inc., White Plains, New York
David Sack, Mark Roffman, Manley Finch, James R. Komorowski

POSTER NO. 168 **CORRELATES OF CLINICIAN RATED AND SELF REPORT MEASURES OF DEPRESSION SYMPTOMATOLOGY IN PATIENTS RECEIVING ECT**
Mustafa M. Husain, University of Texas Southwestern Medical Center at Dallas, Texas
Shawn M. McClintock, Euncil Yim, Martina Mueller, Daniel Wandrey, Rebecca Knapp, Keith Rasmussen, Georgios Petrides, Teresa Rummans, Melanie Biggs, Hilary Bernstein, Max Fink, A. John Rush, Charles Kellner

**Indicates New Investigator Awardee*

POSTER NO. 169 **ESCITALOPRAM TREATMENT OF SSRI NON-RESPONDERS CAN LEAD TO REMISSION IN PATIENTS WHO FAIL INITIAL SSRI THERAPY**
Dan L. Zimbroff, Pacific Clinical Research Medical Group, Upland, California
Anjana Bose, Dayong Li

POSTER NO. 170 **FRONTAL EEG PREDICTS CLINICAL RESPONSE TO SSRI TREATMENT IN MDD**
Dan Iosifescu, Depression Clinical and Research Program, Massachusetts General Hospital / Harvard Medical School, Boston, MA
Scott Greenwald, Philip Devlin, Jonathan Alpert, Sarah Hamil, Maurizio Fava

***POSTER NO. 171** **THE RELATIONSHIP BETWEEN EARLY CHANGES IN THE HAMD-17 ANXIETY/SOMATIZATION FACTOR ITEMS AND TREATMENT OUTCOME AMONG DEPRESSED OUTPATIENTS**
Amy H. Farabaugh, Massachusetts General Hospital, Boston, MA
David Mischoulon, Maurizio Fava, Shirley Wu, Timothy Petersen, Alessandra Mascarini, Eliana Tossani, Jonathan Alpert

POSTER NO. 172 **PATIENT SATISFACTION WITH PHYSICIAN USE OF A COMPUTER-BASED CLINICAL DECISION SUPPORT SYSTEM(CDSS) DURING TREATMENT FOR A PSYCHIATRIC DISORDER**
Shaily Jain, University of Texas Southwestern Medical Center, Dallas, Texas

POSTER NO. 173 **MODAFINIL AS ANTIDEPRESSANT AUGMENTATION THERAPY IN MAJOR DEPRESSIVE DISORDER (MDD)**
Maurizio Fava, Massachusetts General Hospital, Boston, Massachusetts
Michael E. Thase, Charles DeBattista

POSTER NO. 174 **RELATIVE SENSITIVITY OF THE MONTGOMERY-ASBERG DEPRESSION RATING SCALE, THE HAMILTON DEPRESSION RATING SCALE, AND THE CLINICAL GLOBAL IMPRESSIONS RATING SCALE IN ANTIDEPRESSANT CLINICAL TRIALS**
Russell L. Kolts, Department of Psychology, Eastern Washinton University, Cheney, WA
Arif Khan, Amy E. Brodhead, Walter A. Brown

POSTER NO. 175 **A DIRECT COMPARISON OF DEPRESSED PATIENTS FROM PRIMARY CARE VERSUS SPECIALTY CARE SETTINGS: PRELIMINARY RESULTS FROM STAR*D**
Bradley N. Gaynes, University of North Carolina, Chapel Hill, North Carolina
A. John Rush, Madhukar Trivedi, Steven R. Wisniewski, G. K. Balasubramani, Donald C. Spencer, Timothy Petersen, Michael Klinkman, Diane Warden, Robert N. Golden

POSTER NO. 176 **SEVERITY OF DEPRESSIVE SYMPTOMS AND RESPONSE TO ANTIDEPRESSANTS AND PLACEBO IN ANTIDEPRESSANT TRIALS**
Walter A. Brown, Department of Psychiatry, Brown University, Providence, Rhode Island/ Department of Psychiatry, Tufts University, Boston, Massachusetts
Arif Khan, Amy E. Brodhead, Russell L. Kolts

POSTER NO. 177 **DOES SMOKING INHIBIT PLACEBO RESPONSE? A RETROSPECTIVE ANALYSIS OF THE EFFECTS OF SMOKING STATUS IN DEPRESSION CLINICAL TRIALS**
Steven A. Gelwicks, Eli Lilly and Company
David J. DeBrota, Craig H. Mallinckrodt

POSTER NO. 178 **ASSESSMENT OF ANHEDONIA IN DEPRESSED AND IN HEALTHY INDIVIDUALS: EXAMINING THE VALIDITY OF THE SNAITH-HAMILTON PLEASURE SCALE**
Rezvan Ameli, Mood and Anxiety Disorders Program, National Institute of Mental Health
Kathleen Holmes, Carlos A. Zarate, Jr., Dennis S. Charney

POSTER NO. 179 **SENSITIVITY TO TREATMENT DIFFERENCES IN HIGH ENTRY SCORE VERSUS LOW ENTRY SCORE SUBGROUPS IN DEPRESSION CLINICAL TRIALS**
David J. DeBrota, Eli Lilly and Company, Indianapolis, Indiana
Steven C. Gelwicks, Craig H. Mallinckrodt, William Z. Potter

**Indicates New Investigator Awardee*

NCDEU 2004 POSTER ABSTRACTS

Poster Number Index

POSTER NO. 180 **ASSESSING DEPRESSION: HOW MUCH TIME AND EFFORT DOES IT TAKE VIA INTERACTIVE VOICE RESPONSE (IVR)?**
James C. Mundt, Healthcare Technology Systems, Inc., Madison, Wisconsin
Ken Rahn, David J. DeBrota, John H. Greist

***POSTER NO. 181** **BODILY PAIN PREDICTS POOR ANTIDEPRESSANT RESPONSE IN DEPRESSED ELDERLY PRIMARY CARE PATIENTS**
Jordan F. Karp, Department of Psychiatry, University of Pittsburgh School of Medicine
Benoit Mulsant, Amy Begley, Martha L. Bruce, Thomas R. Ten Have, Ira R. Katz, George S. Alexopoulos, Charles F. Reynolds III

POSTER NO. 182 **COMPLETE SOMATIC SYMPTOM RESOLUTION WITH VENLAFAXINE OR SSRIS**
Jeff Musgnung, Wyeth Research, Collegeville, Pennsylvania
Richard Entsuah

POSTER NO. 183 **RESEARCH DESIGN FEATURES AND PATIENT CHARACTERISTICS RELATED TO ANTIDEPRESSANT CLINICAL TRIAL OUTCOME**
Arif Khan, Northwest Clinical Research Center, Bellevue, Washington/Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina
Russell L. Kolts, Michael E. Thase, K. Ranga Rama Krishnan, Walter A. Brown

POSTER NO. 184 **STAR*D SAFETY MONITORING: LESSONS FROM A LARGE HYBRID STUDY OF DEPRESSION**
Andrew A. Nierenberg, Massachusetts General Hospital, Boston, Massachusetts
Madhukar H. Trivedi, Louise Ritz, Stephen Wisniewski, Fred Quitkin, Diane Stegman, Diane Burroughs, John Greist, Maurizio Fava, A. John Rush

POSTER NO. 185 **A COMPARISON OF FACE-TO-FACE AND REMOTE ADMINISTRATION OF THE HAMILTON DEPRESSION RATING SCALE VIA VIDEOCONFERENCING**
Kenneth Kobak, MedAvante/RTA, Madison, Wisconsin

POSTER NO. 186 **COMPARATIVE EFFICACY OF SERTRALINE AND VENLAFAXINE-XR IN MAJOR DEPRESSION**
R. D'Souza, Mental Health Research Institute of Victoria, Australia
A. Sir, T. George, S. Uguz, A. Martin, W. Lam

POSTER NO. 187 **MAINTENANCE TREATMENT WITH ESCITALOPRAM PREVENTS RECURRENCE OF DEPRESSIVE EPISODES**
Susan G. Kornstein, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA
Anjana Bose, Dayong Li

POSTER NO. 188 **COMPARATIVE EFFICACY OF SERTRALINE VERSUS VENLAFAXINE-XR IN ANXIOUS-DEPRESSION**
A. Sir, Dicle University Medical Faculty, Department of Psychiatry, Turkey
T. George, S. Uguz, R. D'Souza, E. Malouf, T. Burt

POSTER NO. 189 **RESULTS FROM THE ARISE-RD (AUGMENTATION WITH RISPERIDONE IN RESISTANT DEPRESSION) TRIAL**
Amy Loescher, CNS Medical Affairs, Janssen Pharmaceutica Products, L.P., Titusville, New Jersey
Mark H. Rapaport, Carla M. Canuso, Frederic Rouillon, Jean Leblanc, Alan Young, Cynthia A. Bossie, Ibrahim Turkoz, Georges M. Gharabawi, The ARISe-RD Study Group

POSTER NO. 190 **APOE4 ALLELE INFLUENCES ANTIDEPRESSANTS' COGNITIVE EFFECTS IN THE ELDERLY**
Ruth O'Hara, Stanford University, Department of Psychiatry, Stanford, California
Alan Schatzberg, Steven B. Hollander, William Lapp, Lee Boyle, Heidi Rodrigues, Helena C. Kraemer, Greer M. Murphy, Jr.

**Indicates New Investigator Awardee*

POSTER NO. 191 **AN OPEN-LABEL, RATER BLINDED STUDY OF ARIPIPRAZOLE AS AN AUGMENTATION AGENT IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION**
Prakash S. Masand, Thomas Jefferson University, Department of Psychiatry, Philadelphia, PA
Rajnish Mago, Ashwin A. Patkar, Marja Evenden, Kathleen Peindl, Cynthia Purcell

POSTER NO. 192 **ASSESSMENT OF ANTIDEPRESSANT EFFECTIVENESS IN THREE SUCCESSIVE TRIALS**
Frederic M. Quitkin, New York State Psychiatric Institute, New York, New York
Jonathan W. Stewart, Patrick J. McGrath, Donald F. Klein

POSTER NO. 193 **DOUBLE-BLIND DOSE-FINDING STUDY OF DOCOSAHEXANOIC ACID (DHA) IN MAJOR DEPRESSIVE DISORDER**
David Mischoulon, Depression Clinical and Research Program, Massachusetts General Hospital, Boston
Jessica Murakami, Yasmin Mahal, Catherine Best, Michael Laposata, Andrew Nierenberg, Maurizio Fava, Jonathan Alpert

POSTER NO. 194 **A ONE-YEAR LONGITUDINAL STUDY OF VNS THERAPY IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION**
A. John Rush, University of Texas Southwestern Medical Center, Dallas, Texas
Harold A. Sackeim, Lauren B. Marangell, Mark S. George

POSTER NO. 195 **COMPLETE REMISSION OF INDIVIDUAL SYMPTOMS AMONG DEPRESSED PATIENTS WITH SEVERE SYMPTOMS AT BASELINE**
Richard Entsuah, Wyeth Research, Collegeville, Pennsylvania

POSTER NO. 196 **TOLERABILITY OF CONTROLLED RELEASE PAROXETINE IN PATIENTS PREVIOUSLY INTOLERANT TO SSRI/SNRI THERAPY**
Cornelius Pitts, GlaxoSmithKline, King of Prussia, Pennsylvania
Desiree M. Schaefer, Lee D. Ruggiero, Malini K. Iyengar, Alan Lipschitz

POSTER NO. 197 **DEPRESSION REMISSION RATES AMONG PATIENTS TREATED WITH VENLAFAXINE XR OR SSRIS USING TREATMENT ALGORITHMS**
Jeff Musgnung, Wyeth Research, Collegeville, Pennsylvania
Isma Benattia, Jay Graepel

POSTER NO. 198 **IMPACT OF ESCITALOPRAM VERSUS NORETHINDRONE ACETATE AND ETHINYL ESTRADIOL ON DEPRESSION, VASOMOTOR SYMPTOMS, AND QUALITY OF LIFE IN PERI AND POSTMENOPAUSAL WOMEN: A RANDOMIZED TRIAL**
Claudio N. Soares, Perinatal Psychiatry Program, Massachusetts General Hospital, Boston, MA
Helga C. Arsenio, Bettina Bankier, Paolo Cassano, Laura F. Petrillo, Hannah M. Gottschall, Lee S. Cohen

POSTER NO. 199 **ANTIDEPRESSANT USE IN VETERANS WITH HEPATITIS C**
Julie Nelligan, Northwest Hepatitis C Resource Center/Portland VA Medical Center
David W. Indest, Aaron D. Blackwell, Anna W. Saski, Marian Fireman, Peter Hauser

POSTER NO. 200 **MULTI-SITE STUDY OF OUTPATIENT MULTIPLE MEDICATION USE IN RELATION TO AGE AND ANTIDEPRESSANT DRUG USE**
Beryl Silkey, Via Christi Research Institute, Wichita, Kansas
Sheldon H. Preskorn, Amanda L. Golbeck, Rozina Shah, Melissa Neff, Teresa L. Jones, Joe Choi

POSTER NO. 201 **COMPARATIVE EFFICACY OF SERTRALINE VERSUS VENLAFAXINE-XR IN SEVERE DEPRESSION**
R. D'Souza, Mental Health Research Institute of Victoria, Australia
T. George, S. Uguz, A. Sir, E. Malouf, T. Burt

POSTER NO. 202 **THE POTENTIAL FOR CLINICALLY SIGNIFICANT DRUG-DRUG INTERACTIONS IN PATIENTS RECEIVING CYP 2D6 MODEL SUBSTRATE/DRUGS AND FLUOXETINE/PAROXETINE OR SERTRALINE**
Sheldon Preskorn, University of Kansas School of Medicine, Wichita, Kansas
Beryl Silkey, Amanda Golbeck, Rozina Shah, Melissa Neff, Joe Choi

NCDEU 2004 POSTER ABSTRACTS

Poster Number Index

POSTER NO. 203 **ESCITALOPRAM IMPROVES SOMATIC SYMPTOMS OF DEPRESSION**
Mark H. Rapaport, Cedars-Sinai Medical Center, Department of Psychiatry, Los Angeles, California
Anjana Bose, Khalil Saikali

***POSTER NO. 204** **CHANGES IN BRAIN FUNCTION DURING PLACEBO LEAD-IN AND TREATMENT OUTCOME IN CLINICAL TRIALS FOR MAJOR DEPRESSION**
Aimee M. Hunter, Behavioral Pharmacology Laboratory, University of California, Los Angeles, CA
Andrew F. Leuchter, Ian A. Cook, Melinda L. Morgan

POSTER NO. 205 **COMPARING METHODOLOGIES FOR ASSESSING ONSET OF ACTION IN NEUROPSYCHIATRIC CLINICAL TRIALS**
Craig H. Mallinckrodt, Eli Lilly and Company, Indianapolis, Indiana
Michael J. Detke, Christopher Kaiser, John Watkin, Geert Molenberghs, Raymond J. Carroll

POSTER NO. 206 **COMPARATIVE PREVALENCE OF PSYCHOTROPIC MEDICATION FOR YOUTH: MEDICAID VERSUS PRIVATE INSURANCE**
Julie Zito, University of Maryland, Baltimore, Maryland

POSTER NO. 207 **ADJUNCT MODAFINIL REDUCES ANTIDEPRESSANT-INDUCED SEDATION IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER**
Nikhil Nihalani, Department of Psychiatry, SUNY Upstate Medical University, Syracuse, New York
Thomas L. Schwartz, Kimberly Cole, Geoffrey Hopkins, Mahai Simonescu, Nicole Jones

POSTER NO. 208 **FLEXIBLE DOSE ARIPIPRAZOLE IN PSYCHOSIS OF ALZHEIMER'S DEMENTIA (AD)**
Dusan Kostic, BMS, Lawrenceville, New Jersey
Christopher Breder, Rene Swanink, Robert McQuade, Taro Iwamoto, William Carson, Elyse Stock

POSTER NO. 209 **ANTIDEPRESSANT TRENDS AMONG CHILDREN AND ADOLESCENTS DIAGNOSED WITH DEPRESSION: 1990-2001**
Tracy L. Skaer, Department of Health Policy and Administration, Washington State University, Pullman, Washington/Pharmacoeconomics and Pharmacoepidemiology Research Unit, Washington State University, Pullman, Washington
David A. Sclar, Linda M. Robison

POSTER NO. 210 **ESCITALOPRAM IN THE TREATMENT OF COMPULSIVE BUYING DISORDER AND KLEPTOMANIA**
Lorrin M. Koran, Stanford University Medical Center
Brent Solvason, Nona Gamel, Emily Smith, Helen W. Chuong, Elias Aboujaoude

POSTER NO. 211 **ESTABLISHING TECHNOLOGY-BASED COMMUNICATIONS IN THE SEQUENCED TREATMENT ALTERNATIVES TO RELIEVE DEPRESSION (STAR*D) PROJECT**
Stephen R. Wisniewski, University of Pittsburgh
Heather Eng, Leslie Meloro, Robert Gatt, Louise Ritz, M.B.A., Diane Stegman, Madhukar Trivedi, Melanie M. Biggs, Edward Friedman, Kathy Shores-Wilson, Diane Warden, A. John Rush

POSTER NO. 212 **A PRE AND POST ANALYSIS OF CLOZAPINE BLOOD LEVELS AND CLINICAL GLOBAL IMPRESSIONS FOR SUBJECTS SWITCHED FROM NOVARTIS BRAND CLOZARIL TO IVAX BRAND CLOZAPINE**
John G. Sonnenberg, Uptown Research Institute, Chicago, Illinois
Michael J. Reinstein, Sangarapillai C. Mohan, Maxim A. Chasanov, Shephali Patel, Virgie McCloud

POSTER NO. 213 **IMPLEMENTATION OF A COMPUTERIZED TREATMENT ALGORITHM FOR DEPRESSION IN REAL WORLD PRACTICE**
Madhukar H. Trivedi, University of Texas Southwestern Medical Center, Dallas, Texas
David W. Morris, Bruce D. Grannemann, Janet K. Kern

POSTER NO. 214 **A COMPREHENSIVE RETROSPECTIVE STUDY OF ASSOCIATIONS BETWEEN DIABETES AND TREATMENT WITH RISPERIDONE, OLANZAPINE, QUETIAPINE, AND CONVENTIONAL ANTIPSYCHOTICS**
Frank R. Gianfrancesco, HECON Associates, Inc., Montgomery Village, Maryland
Ruey-hua Wang, Henry Nasrallah

**Indicates New Investigator Awardee*

POSTER NO. 215 **IMPROVEMENT IN QUALITY OF LIFE WITH RISPERIDONE AUGMENTATION IN TREATMENT-RESISTANT DEPRESSION**
Ibrahim Turkoz, Janssen Pharmaceutica Products, L.P., Titusville, New Jersey/CNS Network Garden Grove, California
David Walling, Marcia Rupnow, Carla M. Canuso, Georges Gharabawi, Mark H. Rapaport

POSTER NO. 216 **COURSE OF WEIGHT & METABOLIC BENEFITS 1 YEAR AFTER SWITCHING TO ZIPRASIDONE**
Peter J. Weiden, Department of Psychiatry, SUNY Downstate, Brooklyn, New York
David G. Daniel, Antony Loebel, Lewis Warrington, Judith Dunn, Stephen Murray

POSTER NO. 217 **THE GRID HAMD: AVAILABILITY OF A NEW STANDARDIZED METHOD FOR THE ASSESSMENT OF DEPRESSION**
Amir Kalali, ISCDD, San Diego, California
Per Bech, Nina Engelhardt, Ken Evans, Ken Kobak, Josh Lipsitz, Jason Olin, Jay Pearson, Margaret Rothman, Janet B.W. Williams

POSTER NO. 218 **DIFFERENTIAL EFFECTS OF ANTIPSYCHOTIC MEDICATIONS ON OVERWEIGHT PEOPLE WITH SEVERE MENTAL ILLNESS IN A PSYCHOSOCIAL WEIGHT LOSS PROGRAMME**
Ruth Ohlsen, Section of Neurochemical Imaging and Psychiatry, Institute of Psychiatry, De Crespigny Park, London, United Kingdom

POSTER NO. 219 **EFFECTS OF MOOD STABILIZER TREATMENT ON MOOD EPISODE RELAPSE AND RECURRENCE IN BIPOLAR DISORDER**
Joseph Goldberg, Zucker Hillside Hospital/Long Island Jewish Medical Center
Terrence Ketter, Joseph Calabrese, Trisha Suppes, Mark Frye, Robin White

POSTER NO. 220 **ZIPRASIDONE VERSUS OLANZAPINE: CONTRASTS IN CHD RISK**
Megan C. Leaderer, Pfizer, Inc., New York, New York
David J. Harrison, Antony Loebel, Stephen Murray

POSTER NO. 221 **REFERENCED-EEG IN THE TREATMENT OF EATING DISORDERS**
Mark Schiller, University of California, San Francisco, California
W. Hamlin Emory, Stephen C. Suffin

POSTER NO. 222 **POST-HOSPITALIZATION CONTINUITY OF ANTIPSYCHOTIC PHARMACOTHERAPY AMONG MEDICAID RECIPIENTS**
Sheila R. Botts, University of Kentucky College of Pharmacy, Lexington, Kentucky
Robert A. Littrell, Hyui Hines

POSTER NO. 223 **DOSE-RANGING STUDY OF ARIPIPRAZOLE IN PATIENTS WITH ALZHEIMER'S DEMENTIA**
Christopher Breder, BMS, Wallingford, Connecticut
Dusan Kostic, Rene Swanink, Ronald Marcus, Taro Iwamoto, William Carson, Robert McQuade

POSTER NO. 224 **MALE SCHIZOPHRENIC PATIENTS HAVE IMPAIRMENT IN PROCESSING SPATIAL INFORMATION FROM DISSOCIATED SPATIAL FRAMES OF REFERENCE**
Miranda H. Chakos, SUNY Downstate Medical Center, Brooklyn, New York
Yegeviy Gelfand, Narender Dargani, Andre Fenton

POSTER NO. 225 **DRUG SENSITIVITY IN THE AGING BRAIN AND SUBCLINICAL STRUCTURAL BRAIN DISEASE**
Ian A. Cook, Behavioral Pharmacology Laboratory, UCLA Neuropsychiatric Institute and Hospital/Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, California
Andrew F. Leuchter, Melinda L. Morgan, Michelle J. Abrams, Laura Mickes, Barbara Siegman

NCDEU 2004 POSTER ABSTRACTS

Poster Number Index

POSTER NO. 226 **RELATIONSHIP OF ANTIPSYCHOTICS TO NEW CASES OF DIABETES MELLITUS**
Leslie L. Citrome, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, New York/New York University School of Medicine, New York, New York
Ari B. Jaffe, Jerome Levine, Baerbel Allingham, James Robinson

POSTER NO. 227 **EFFECTS OF PNP-12 ON COGNITIVE PERFORMANCE IN AGE-ASSOCIATED MEMORY IMPAIRMENT**
Thomas H. Crook, Psychologix, Inc., Fort Lauderdale, Florida
Steven H. Ferris, Martha Laredo, X. Anton Alvarez, Herbert Moessler

POSTER NO. 228 **QUETIAPINE VERSUS HALOPERIDOL DECANOATE FOR LONG-TERM TREATMENT OF SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER**
Ira D. Glick, Stanford University School of Medicine, Department of Psychiatry and Behavioral Sciences, Stanford, California
Stephen R. Marder

POSTER NO. 229 **PHARMACOTHERAPY RECEIVED BY INDIVIDUALS WITH BODY DYSMORPHIC DISORDER**
Katharine A. Phillips, Butler Hospital/Brown University, Providence, Rhode Island
Maria E. Pagano, Christina Fay, William Menard

POSTER NO. 230 **LONG-TERM COGNITIVE IMPROVEMENT IN PATIENTS SWITCHED TO ZIPRASIDONE**
Antony Loebel, Pfizer, Inc., New York, New York
Evan Batzar, Stephen Murray, Philip D. Harvey

POSTER NO. 231 **A CHART-REVIEW STUDY OF SRI CONTINUATION TREATMENT VERSUS DISCONTINUATION IN BODY DYSMORPHIC DISORDER**
Satyam Jain, Butler Hospital/Brown University, Providence, Rhode Island
Jon E. Grant, William Menard, Stephen Cerasoli, Katharine A. Phillips

POSTER NO. 232 **GLUCOSE METABOLISM IN SCHIZOPHRENIA PATIENTS TREATED WITH ATYPICAL ANTIPSYCHOTICS: A FREQUENT SAMPLED INTRAVENOUS GLUCOSE TOLERANCE TEST AND MINIMAL MODEL ANALYSIS**
David C. Henderson, Massachusetts General Hospital, Harvard Medical School, Boston, MA
David Allison, Enrico Cagliero, Tara B. Daley, Christina Borba, Paul Copeland, Ellen Anderson, Doug Hayden, David Schoenfeld, Donald C. Goff

POSTER NO. 233 **SEXUAL FUNCTION AND PROLACTIN LEVELS: A RANDOMIZED DOUBLE-BLIND 12-WEEK STUDY OF QUETIAPINE, RISPERIDONE OR FLUPHENAZINE**
Deanna L. Kelly, Maryland Psychiatric Research Center, University of Maryland, Baltimore, MD
Robert R. Conley, Rhonda Reynolds

POSTER NO. 234 **PREDOMINANCE OF PSYCHIATRIC-BASED REASONS FOR ANTIPSYCHOTIC TREATMENT DISCONTINUATION**
Sajjad Khan, Eli Lilly and Company, Indianapolis, Indiana
Hong Liu-Seifert, Bruce J. Kinon

***POSTER NO. 235** **RILUZOLE: AN INVESTIGATION OF THE ANTIDEPRESSANT EFFICACY OF AN ANTIGLUTAMATERGIC AGENT WITH NEUROTROPHIC PROPERTIES**
Jennifer L. Payne, National Institute of Mental Health, Bethesda, Maryland
Carlos A. Zarate, Kirk Denicoff, Jorge A. Quiroz, Jonathan Sporn, Dennis S. Charney, Husseini K. Manji

POSTER NO. 236 **DETERMINING OPTIMUM MEDICATION IN SCHIZOPHRENIC PATIENTS: DEVELOPMENT OF A STATISTICAL MODEL**
David L. Van Brunt, Eli Lilly and Company, Indianapolis, Indiana
P. Joseph Gibson, Hong Lui-Seifert, Robert L. Obenchain, Saeeduddin Ahmed

**Indicates New Investigator Awardee*

POSTER NO. 237 **ZIPRASIDONE: LONG-TERM POST-SWITCH EFFICACY IN SCHIZOPHRENIA**
George M. Simpson, LAC + USC Medical Center, Los Angeles, CA
Peter J. Weiden, Antony Loebel, Lewis Warrington, Ruoyong Yang

POSTER NO. 238 **THE RELATIONSHIP BETWEEN COGNITIVE MEASURES AND FUNCTIONAL OUTCOMES IN SCHIZOPHRENIA**
Gahan Pandina, Janssen Pharmaceutica Products, L.P., Titusville, New Jersey
Georges Gharabawi, Stephen Rodriguez, Robert Lasser

POSTER NO. 239 **DOSING OF SECOND GENERATION ANTIPSYCHOTIC MEDICATION IN A STATE HOSPITAL SYSTEM**
Leslie L. Citrome, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, New York/New York University School of Medicine, New York, New York
Ari B. Jaffe, Jerome Levine

***POSTER NO. 240** **ADHERENCE TO CLOZAPINE: EFFECTS OF REDUCED FREQUENCY OF HEMATOLOGIC MONITORING**
Nick C. Patel, College of Pharmacy, The University of Texas at Austin, Texas/Texas Department of Mental Health and Mental Retardation, Austin, Texas
M. Lynn Crismon, Michael T. Johnsrud, Alexander L. Miller

POSTER NO. 241 **DISTRESS WITH MEDICATION SIDE EFFECTS AMONG PERSONS WITH SEVERE MENTAL ILLNESS**
Nancy H. Covell, University of Connecticut/Connecticut Department of Mental Health and Addiction Service, Hartford, CT
Ellen Weissman, Bonnie Schell, Brian McCorkle, Tom Summerfelt, Peter Weiden, Susan M. Essock

POSTER NO. 242 **EFFECT OF ANTIPSYCHOTIC CHANGE ON WEIGHT IN MINORITIES**
Humberto Marin, UMDNJ/Robert Wood Johnson Medical School, Piscataway, New Jersey
Matthew Menza, Anthony Tobia

POSTER NO. 243 **REVIEW OF INPATIENT USE OF ANTIPSYCHOTIC DRUGS AT McLEAN HOSPITAL BETWEEN 1989 AND 2002**
Kate V. Fogarty, McLean Hospital, Belmont, Massachusetts
Franca Centorrino, Paola Salvatore, Gabriele Sani, John Hennen, Ross J. Baldessarini

POSTER NO. 244 **QUETIAPINE FOR AGITATION AND AGGRESSION IN BIPOLAR MANIA**
Edna Stirewalt, Medical College of Georgia, Augusta, Georgia
Peter Buckley, Björn Paulsson Södertälje, Martin Brecher

POSTER NO. 245 **INSIGHT IN STABLE PATIENTS WITH SCHIZOPHRENIA RECEIVING LONG-ACTING RISPERIDONE**
Georges M. Gharabawi, CNS Medical Affairs, Janssen Pharmaceutica Products, L.P., Titusville, NJ
Cynthia A. Bossie, Robert A. Lasser, Young Zhu

POSTER NO. 246 **COGNITIVE EFFECTS OF ZIPRASIDONE IN FIRST EPISODE PSYCHOSIS: AN fMRI STUDY**
Tonmoy Sharma, Clinical Neuroscience Research Centre, Dartford, United Kingdom
Veena Kumari

POSTER NO. 247 **INCREASED AMYGDALAR ACTIVATION AFTER SECRETIN ADMINISTRATION: AN fMRI STUDY**
Staci A. Gruber, Cognitive Neuroimaging Laboratory, McLean Hospital, Harvard Medical School
Jadwiga Rogowska, Patrice Rioux, Karen Juaregui, Jim Rusche, Deborah A. Yurgelun-Todd

POSTER NO. 248 **THE GAIN ACCEPTANCE APPROACH: A NOVEL PSYCHOSOCIAL APPROACH TO SUPPORTING PATIENT ACCEPTANCE OF A LONG-ACTING INJECTABLE ANTIPSYCHOTIC**
Ronald Urioste, Janssen Medical Affairs, L.L.C., Titusville, NJ
Xavier Amador, Robert Lasser, Georges Gharabawi

**Indicates New Investigator Awardee*

NCDEU 2004 POSTER ABSTRACTS

Poster Number Index

POSTER NO. 249 **IM ZIPRASIDONE IN THE PSYCHIATRIC ER: EXPANDED SAMPLE**
Andrew Francis, State University of New York (SUNY) Stony Brook, Stony Brook, New York
Robert Southard, Steven G. Klotz, Horacio Preval

POSTER NO. 250 **MUTATION STUDIES OF PREGABALIN BINDING AND PHARMACOLOGY IN VIVO AT ALPHA2-DELTA PROTEINS**
Charles P. Taylor, Pfizer Global Research and Development, Ann Arbor, Michigan
Ti-Zhi Su, James Offord, Mark J. Field, Scott Baron, Stevin Zorn

POSTER NO. 251 **MEDICATION-SPECIFIC CORRELATES OF RELAPSE RISK IN SCHIZOPHRENIA**
Lisa Jaton, Eli Lilly and Company, Indianapolis, Indiana
Walter Deberdt, , John Csernansky, Peter F. Buckley, Jozef Peuskens, David L. Van Brunt, Angela Hill, Hong Liu-Seifert

POSTER NO. 252 **SAFETY, TOLERABILITY, AND PATIENT FUNCTIONAL STATUS WITH LONG-TERM MODAFINIL IN CHRONIC SHIFT WORK SLEEP DISORDER**
Russell Rosenberg, Northside Hospital Sleep Medicine Institute, Atlanta, Georgia
Bruce C. Corser, Milton K. Erman, David F. Dinges, Charles A. Czeisler, James K. Walsh, Thomas Roth

POSTER NO. 253 **MANUAL-GUIDED USE OF LONG-ACTING RISPERIDONE IN COMMUNITY-BASED SETTINGS**
Stephen Rodriguez, Janssen Medical Affairs, LLC
Robert Jones, John P. Docherty, Ibrahim Turkoz, Robert A. Lasser

POSTER NO. 254 **EFFICACY AND TOLERABILITY OF INDIPLON-IR FOR CHRONIC INSOMNIA: RESULTS USING BEDTIME AND MIDDLE OF THE NIGHT DOSING STRATEGIES**
R. Rosenberg, Northside Hospital, Atlanta, Georgia
J.K. Walsh, T. Roth, D.A. Lankford, P. Jochelson, for the Indiplon Study Group

POSTER NO. 255 **DIVALPROEX SODIUM EXTENDED RELEASE FOR ACUTE TREATMENT OF SCHIZOPHRENIA: A RETROSPECTIVE CHART REVIEW**
Arnaldo Negron, Capital Health System, Trenton, New Jersey/UMDNJ-Robert Wood Johnson Medical School, Piscataway, New Jersey

POSTER NO. 256 **LUTEAL PHASE VS. SYMPTOM-ONSET DOSING WITH ESCITALOPRAM FOR PREMENSTRUAL DYSPHORIC DISORDER: A PRELIMINARY STUDY**
Ellen W. Freeman, Department of Obstetrics/Gynecology and the Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania
Steven J. Sondheimer, Mary D. Sammel, Tahmina Ferdousi

POSTER NO. 257 **PILOT EVALUATION OF ATOMOXETINE AUGMENTATION OF CLOZAPINE AS A TREATMENT FOR THE COGNITIVE SYMPTOMS OF SCHIZOPHRENIA**
Jeffrey D. Lightfoot, Indiana University School of Medicine, Indianapolis, Indiana
Michael Webber, Fredrick Malloy, Timothy Steadman, Anantha Shekhar

POSTER NO. 258 **IMMEDIATE VERSUS CONTROLLED RELEASE PAROXETINE: PK PROFILES AT STEADY STATE AND IMPACT OF CYP2D6 METABOLIZER STATUS**
David J. Carpenter, Medical University of South Carolina, Charleston, South Carolina
C. Lindsay DeVane, Alan Lipschitz, Philip Perera

POSTER NO. 259 **IMPACT OF RISPERIDONE TABLET-SPLITTING ON CLINICAL OUTCOMES AND MEDICATION ADHERENCE**
Ellen Weissman, Bronx VA Medical Center, Bronx, New York
Mara Kushner, Cornelia Dellenbaugh

POSTER NO. 260 **MULTIPLE RATERS IN CLINICAL TRIALS: A BETTER RESEARCH DESIGN?**
Wendy J. Bourg, Summit Research Network, Portland, Oregon
Ward T. Smith, Peter D. Londborg, Robert J. Bielski, John R. Painter, Vince Glaudin

POSTER NO. 261 **TOLERANCE TO SOMNOLENCE WITH QUETIAPINE: PRECLINICAL MECHANISMS AND CLINICAL EVIDENCE**
Jeffrey M. Goldstein, AstraZeneca Pharmaceuticals, LP, Wilmington, Delaware
Kate Zhong

POSTER NO. 262 **DOUBLE-BLIND COMPARISON OF ESCITALOPRAM AND PAROXETINE IN THE LONG-TERM TREATMENT OF GENERALIZED ANXIETY DISORDER**
Robert J. Bielski, Forest Labs, Jersey City, New Jersey
Anjana Bose, Chung-Chi Chang, Jane Ruby

POSTER NO. 263 **NORMALIZATION OF COGNITIVE FUNCTION WITH LONG-TERM ZIPRASIDONE OR OLANZAPINE**
Philip C. Harvey, Mount Sinai School of Medicine, New York, New York
Christopher R. Bowie, Antony Loebel, Lewis Warrington

POSTER NO. 264 **ARIPIPRAZOLE VERSUS PLACEBO IN PATIENTS WITH ACUTE MANIC OR MIXED EPISODE**
Robert McQuade, BMS, Lawrenceville, New Jersey
Raymond Sanchez, Ronald Marcus, Mary Kujawa, Donald Archibald, William Carson, Taro Iwamoto

POSTER NO. 265 **MULTICENTER STUDY OF THE SAFETY AND EFFICACY OF THE MELATONIN AGONIST LY156735 IN PRIMARY INSOMNIA**
Frank Zemlan, Phase 2 Discovery, Cincinnati, Ohio
Jeff Mulchahey, David Mayleben, Martin Scharf, Russell Rosenberg, Alan Lankford

POSTER NO. 266 **IMPROVEMENT IN GLOBAL FUNCTIONING IN BIPOLAR PATIENTS: RESULTS FROM AN OPEN-LABEL, RISPERIDONE STUDY**
Marcia F.T. Rupnow, Janssen Medical Affairs, LLC, Titusville, New Jersey
Carla M. Canuso, Philip G. Janicak

POSTER NO. 267 **MODAFINIL FOR THE TREATMENT OF EXCESSIVE SLEEPINESS ASSOCIATED WITH CHRONIC SHIFT WORK SLEEP DISORDER**
Thomas Roth, Henry Ford Sleep Disorders Center, Detroit, Michigan
James K. Walsh, Charles A. Czeisler, David F. Dinges

POSTER NO. 268 **THE BURDEN OF DEPRESSION IN PATIENTS WITH BIPOLAR DISORDER**
Anupama A. Krishnan, GlaxoSmithKline, Research Triangle Park, North Carolina
Alex Z. Fu, Sonya D. Harris

POSTER NO. 269 **TRAJECTORY ANALYSIS OF TREATMENT RESPONSE DURING A SIX-MONTH STUDY OF NIGHTLY ESZOPICLONE IN PATIENTS WITH CHRONIC INSOMNIA**
Daniel Buysse, University of Pittsburgh, Pittsburgh, Pennsylvania
P. Wilson, D. Amato, T. Wessel

POSTER NO. 270 **FIRST SIX MONTHS OF INPATIENT ARIPIPRAZOLE USE AT McLEAN HOSPITAL**
Kate V. Fogarty, McLean Hospital, Belmont, Massachusetts
Franca Centorrino, Paola Salvatore, Paola Cimbolli, Terri-Ann Thompson, Ross J. Baldessarini

POSTER NO. 271 **RELAPSE OF DEPRESSION DURING PREGNANCY FOLLOWING DISCONTINUATION OF ANTIDEPRESSANT TREATMENT**
Lee S. Cohen, Perinatal and Reproductive Psychiatry, Massachusetts General Hospital, Boston, MA
Pauline S. Powers, Zachary N. Stowe, Amy M. Loescher, Rita Suri, Jeffrey Newport,
Alison M. Reminick, Susan Mazzei, Ada Loughhead, Bernard H. Harlow

**Indicates New Investigator Awardee*

NCDEU 2004 POSTER ABSTRACTS

Poster Number Index

POSTER NO. 272 **TOLERABILITY AND DISCONTINUATION EFFECTS FOR SERTRALINE VERSUS VENLAFAXINE-XR IN DEPRESSION**
A. Sir, Dicle University Medical Faculty, Department of Psychiatry, Turkey
R. D'Souza, S. Uguz, T. George, F. McIlroy, W. Lam

POSTER NO. 273 **A VALIDATION STUDY OF THE SEXUAL INTEREST AND DESIRE INVENTORY (SIDI)**
Glen R. Wunderlich, Boehringer-Ingelheim, Burlington, Ontario, Canada
Anita Clayton, Taylor Segraves, Sandra Leiblum, Rosemary Basson, Robert Pyke, Terrence Sills, Kenneth Evans

POSTER NO. 274 **USING A SELF-REPORT DEPRESSION SCALE TO IDENTIFY REMISSION IN DEPRESSED OUTPATIENTS**
Mark Zimmerman, Rhode Island Hospital, Providence, Rhode Island
Iwona Chelminski, Michael Posternak

POSTER NO. 275 **REAL-TIME DIGITAL DATA CAPTURE (DDC): A CLINICAL TRIAL TOOL FOR ENHANCING DATA QUALITY AND PROMOTING CLINICAL RATING RELIABILITY**
Ester Salmán, ChiMatrix, L.L.C., New York, New York/The Medical Research Network, L.L.C. New York, New York
Michael R. Liebowitz

POSTER NO. 276 **ANTICONVULSANTS IN PREGNANCY AND LACTATION: DIFFERENCES IN ATTITUDES AND PRACTICE PATTERNS AMONG NEUROLOGISTS AND PSYCHIATRISTS**
Adele C. Viguera, Massachusetts General Hospital, Boston, Massachusetts
Lee S. Cohen, Alison M. Reminick, Rachel Bender, Giselle A. LeBlanc, John Hennen

***POSTER NO. 277** **DIETARY INTAKE PROFILE OF PATIENTS WITH SCHIZOPHRENIA**
Tara B. Daley, Massachusetts General Hospital Schizophrenia Program, Boston, Massachusetts
David C. Henderson, Dana D. Nguyen, Melissa A. Culhane, Pearl M. Louie, Christina Borba, Sarah M. Taber, Donald C. Goff

POSTER NO. 278 **DOUBLE-BLIND COMPARISON OF A FIXED DOSE OF ESCITALOPRAM (10 MG/DAY) AND AN OPTIMAL DOSING REGIMEN OF SERTRALINE (50-200 MG/DAY) IN DEPRESSED PATIENTS**
Anna Stroble, Forest Labs, Jersey City, New Jersey
Arif Khan, William Privitera, Daniel Ventura, Anjana Bose, Qin Wang

POSTER NO. 279 **THE LONG-TERM IMPACT OF MOOD STABILIZERS ON BODY WEIGHT**
Gary Sachs, Harvard University, Boston, Massachusetts
Charles Merideth, Lawrence Ginsberg, Alan Swann, Thomas Thompson, Robin White, Connie Powers

POSTER NO. 280 **COMPARATIVE OVERALL EFFECTIVENESS OF SCHIZOPHRENIA PATIENTS TREATED WITH ATYPICAL ANTIPSYCHOTICS OLANZAPINE VERSUS ARIPIPRAZOLE**
Gilbert J. L'Italien, BMS, Pharmaceutical Research Institute, Wallingford, Connecticut
Rajiv Tandon, Jian Han, Hong Li, Saurabh Ray, William Carson

POSTER NO. 281 **TREATMENT OF PAIN IN FIBROMYALGIA IS DISTINCT FROM TREATMENT OF MOOD**
R. Michael Gendreau, Cypress Bioscience, San Diego, California
Jay D. Kranzler, Srinivas G. Rao, Daniel J. Clauw

POSTER NO. 282 **PHARMACOKINETICS OF LAMOTRIGINE AND OXCARBAZEPINE CO-THERAPY**
John Ascher, GlaxoSmithKline, Research Triangle Park, North Carolina
Jochen Theis, Jagdev Sidhu, Sarah Job, Joanne Palmer

**Indicates New Investigator Awardee*

POSTER NO. 283 **UNDERSTANDING AND ADDRESSING REGULATORY QUESTIONS IN THE USE OF TECHNOLOGY SOLUTIONS TO COLLECT PATIENT REPORTED OUTCOMES DATA**
Keith A. Wesnes, ClinPhone, Inc., Princeton, New Jersey
Bill D. Byrom, John P. Houston

POSTER NO. 284 **CORRELATIONS AND FACTOR STRUCTURES WITHIN DATA FROM CONTEMPORANEOUS INTERACTIVE VOICE RESPONSE SYSTEM AND CLINICIAN ADMINISTRATIONS OF THE HAMILTON DEPRESSION RATING SCALE**
David J. DeBrota, Eli Lilly and Company, Indianapolis, Indiana
James C. Mundt, Jyoti Rayamajhi, John H. Greist

POSTER NO. 285 **ATYPICAL ANTIPSYCHOTICS IN THE TREATMENT OF MANIA: A META-ANALYSIS OF RANDOMIZED, PLACEBO-CONTROLLED COMBINATION THERAPY TRIALS**
Roy H. Perlis, Massachusetts General Hospital/Harvard Medical School, Boston, MA
Jeffrey A. Welge, Robert M.A. Hirschfeld, Paul E. Keck

POSTER NO. 286 **PLACEBO-LEVEL EPS AND AKATHISIA DURING QUETIAPINE TREATMENT FOR MANIA**
Nick Votolato, Ohio State University, Columbus, Ohio
Henry A. Nasrallah

POSTER NO. 287 **SAFETY, TOLERABILITY, AND EFFICACY OF PSILOCYBIN IN TREATMENT REFRACTORY OCD**
Francisco A. Moreno, The University of Arizona, Tucson, Arizona
Christopher B. Wiegand, Keo Taitano, Pedro L. Delgado

POSTER NO. 288 **EFFICACY OF QUETIAPINE IN MANIA ASSOCIATED WITH BIPOLAR DISORDER**
Roger S. McIntyre, University Health Network, Toronto Western Hospital, Toronto, Ontario, Canada
Martin Jones, Björn Paulsson

POSTER NO. 289 **RESPONSE TO MOOD STABILIZERS IN OLDER PATIENTS WITH BIPOLAR I DISORDER**
Martha Sajatovic, Case Western Reserve University School of Medicine, Cleveland, Ohio
Laszlo Gyulai, Gary Evoniuk, Robin White

POSTER NO. 290 **PSYCHOTROPIC UTILIZATION AND CLINICAL PRESENTATION OF HOSPITALIZED VERY-YOUNG CHILDREN**
Sanjeev Pathak, Children's Hospital Medical Center, Division of Child and Adolescent Psychiatry, Cincinnati, Ohio/University of Cincinnati, Department of Psychiatry
Sarah P. Arszman, Erin S. Johns, Arman Danielyan, Alex Smirnov, Robert A. Kowatch

POSTER NO. 291 **SERTRALINE AND VENLAFAXINE IN MAJOR DEPRESSION**
Richard Shelton, Vanderbilt University, Nashville, TN
Mark Rapaport, John Zajecka, Bruce Lydiard, Robert Hirschfeld, Ari Kiev, Alan Gelenberg, Ward Smith

POSTER NO. 292 **THE EFFICACY OF QUETIAPINE IN THE TREATMENT OF DELUSIONAL DISORDER**
Mark G. Opler, Department of Epidemiology, Columbia University, New York, New York
Lewis A. Opler, Jamie A. Mullen

POSTER NO. 293 **RATER EXPERIENCE IN CNS CLINICAL TRIALS**
Stephen Targum, PharmaStar, Wayne, Pennsylvania
Ann Bullinger

POSTER NO. 295 **RACIAL DIFFERENCES IN RESPONSE TO ECT: A COMPARISON OF AFRICAN-AMERI CAN VERSUS CAUCASIAN POPULATIONS**
Rebecca G. Knapp, Medical University of South Carolina, Charleston, SC
Teresa Rummans, Charles Kellner, Mustafa Husain, Georgios Petrides, Shirlene Sampson, Martina Mueller, Hilary Bernstein, Max Fink, Kevin O'Connor, Glenn Smith, Melanie Biggs

NCDEU 2004 POSTER ABSTRACTS

Poster Number Index

POSTER NO. 297 **USE OF GALANTAMINE HBr IN ELECTROCONVULSIVE THERAPY**
John D. Matthews, Massachusetts General Hospital, Boston, Massachusetts
Mark A. Blais, Jessica L. Murakami, Charles A. Welch, Lawrence Park, William Pirl
David Borrelli, Christina M. Gulliver, Maurizio Fava

POSTER NO. 299 **THE USE OF TOPIRAMATE IN PATIENTS WITH EPISODES OF AGGRESSIVE OR IMPULSIVE BEHAVIORS: A REPORT OF SIX CASES**
Susan B. Kay, Psychopharmacology Research Corporation, Farmington Hills, Michigan
Alan H. Rosenbaum, L. M. Hoes, Kellie R. Murry, Tracey L. Stein

POSTER NO. 301 **OXCARBAZEPINE IN PATIENTS WITH IMPULSIVE AGGRESSION**
Jeffrey A. Mattes, Psychopharmacology Research Association of Princeton, Princeton, New Jersey

Adler, Caleb 089
SAFETY AND TOLERABILITY OF QUETIAPINE IN BIPOLAR MANIA

Ameli, Rezvan 178
ASSESSMENT OF ANHEDONIA IN DEPRESSED AND IN HEALTHY INDIVIDUALS: EXAMINING THE VALIDITY OF THE SNAITH-HAMILTON PLEASURE SCALE

Ascher, John 093
A PHARMACOKINETIC INTERACTION STUDY OF LAMOTRIGINE AND OLANZAPINE

Ascher, John 282
PHARMACOKINETICS OF LAMOTRIGINE AND OXCARBAZEPINE CO-THERAPY

Baldassano, Claudia 074
QUETIAPINE IN THE TREATMENT OF DEPRESSIVE SYMPTOMS IN BIPOLAR MANIA

Ball, Susan 047
FACILITATED EXTINCTION OF SOCIAL FEARS WITH D-CYCLOSERINE

Banerjee, Pradeep 143
MEMANTINE PREVENTS Aß1-40-INDUCED APOPTOTIC CELL DEATH IN THE RAT HIPPOCAMPUS

Baskys, Andrius 139
NEUROPROTECTIVE PROPERTIES OF QUETIAPINE: A POSSIBLE MECHANISM IN TREATMENT OF PSYCHOSIS?

Bauer, Michael 103
SLEEP AND MOOD IN PATIENTS TREATED FOR BIPOLAR DISORDER: A TIME SERIES APPROACH

Berlant, Jeffrey 030
ADD-ON AND MONOTHERAPY TOPIRAMATE IN CIVILIANS WITH CHRONIC NON-HALLUCINATORY POSTTRAUMATIC STRESS DISORDER: A PROSPECTIVE OPEN-LABEL STUDY

Bielski, Robert 262
DOUBLE-BLIND COMPARISON OF ESCITALOPRAM AND PAROXETINE IN THE LONG-TERM TREATMENT OF GENERALIZED ANXIETY DISORDER

Bockbrader, Howard 044
PREGABALIN'S PHARMACOKINETIC PROFILE SHOWS MINIMAL DRUG-DRUG INTERACTIONS

Bossie,Cynthia 105
RISK OF MOVEMENT DISORDERS IS LOW IN PEDIATRIC PATIENTS TREATED WITH RISPERIDONE

Botts, Sheila 222
POST-HOSPITALIZATION CONTINUITY OF ANTIPSYCHOTIC PHARMACOTHERAPY AMONG MEDICAID RECIPIENTS

Bourg, Wendy 260
MULTIPLE RATERS IN CLINICAL TRIALS: A BETTER RESEARCH DESIGN?

Bowie, Christopher 094
LONG-TERM COGNITIVE IMPROVEMENT: ZIPRASIDONE VERSUS OLANZAPINE

Bowles, Toya 154
ASSESSMENT OF SEROTONIN TYPE 1A (5-HT1A) RECEPTOR GENOTYPE IN A NORMAL VERSUS A DEPRESSED POPULATION AND THE RELATIONSHIP TO PREDICTABILITY OF ANTIDEPRESSANT RESPONSIVENESS

Brawman-Mintzer, Olga 032
METHODOLOGICAL CONSIDERATIONS IN A GAD TREATMENT TRIAL

NCDEU 2004 POSTER ABSTRACTS

Presenting Author Index

Breder, Christopher 223
DOSE-RANGING STUDY OF ARIPIPRAZOLE IN PATIENTS WITH ALZHEIMER'S DEMENTIA

Brown, Walter 176
SEVERITY OF DEPRESSIVE SYMPTOMS AND RESPONSE TO ANTIDEPRESSANTS AND PLACEBO IN ANTIDEPRESSANT TRIALS

Buysse, Daniel 269
TRAJECTORY ANALYSIS OF TREATMENT RESPONSE DURING A SIX-MONTH STUDY OF NIGHTLY ESZOPICLONE IN PATIENTS WITH CHRONIC INSOMNIA

Calabrese, Joseph 086
USING MOOD STATE TO PREDICT POLARITY OF RELAPSE IN BIPOLAR MAINTENANCE STUDIES

***Cannon, Dara** 156
REDUCED MUSCARINIC CHOLINERGIC2 RECEPTOR BINDING IN BIPOLAR DISORDER USING PET AND [F-18]FP-TZTP

Carmassi, Claudia 159
RECURRING SYMPTOMS ACROSS CONSECUTIVE EPISODES OF MAJOR DEPRESSION

Carpenter, David 258
IMMEDIATE VERSUS CONTROLLED RELEASE PAROXETINE: PK PROFILES AT STEADY STATE AND IMPACT OF CYP2D6 METABOLIZER STATUS

Carson, William 122
SAFETY PROFILE OF ARIPIPRAZOLE IN PSYCHOSIS OF ALZHEIMER'S DEMENTIA: POOLED ANALYSIS

Castilla, Ruby 054
PRELIMINARY RESULTS ON PREGNANCY OUTCOMES IN BIPOLAR WOMEN: DATA FROM THE LAMOTRIGINE PREGNANCY REGISTRY

Castilla, Ruby 065
A LONGITUDINAL 7-YEAR FOLLOW-UP STUDY OF BIPOLAR DISORDER IN A UNIPOLAR COHORT

Cavazzoni, Patrizia 124
INCIDENCE OF MORTALITY DURING ANTIPSYCHOTIC CLINICAL TRIALS OF ELDERLY PATIENTS WITH DEMENTIA

Chakos, Miranda 224
MALE SCHIZOPHRENIC PATIENTS HAVE IMPAIRMENT IN PROCESSING SPATIAL INFORMATION FROM DISSOCIATED SPATIAL FRAMES OF REFERENCE

Chaney, Robert 107
RECRUITMENT OUTCOMES IN CHILD AND ADOLESCENT DEPRESSION

Chung, Henry 108
THE SAFETY AND EFFECTIVENESS OF SERTRALINE FOR THE TREATMENT OF NEURASTHENIA

Citrome, Leslie 226
RELATIONSHIP OF ANTIPSYCHOTICS TO NEW CASES OF DIABETES MELLITUS

Citrome, Leslie 239
DOSING OF SECOND GENERATION ANTIPSYCHOTIC MEDICATION IN A STATE HOSPITAL SYSTEM

Cohen, Lee 271
RELAPSE OF DEPRESSION DURING PREGNANCY FOLLOWING DISCONTINUATION OF ANTIDEPRESSANT TREATMENT

**Indicates New Investigator Awardee*

Coleman, Julie 145
A 26-WEEK, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF DIVALPROEX SODIUM ER AUGMENTATION OF DONEPEZIL FOR COGNITION AND BEHAVIOR IN MILD/MODERATE ALZHEIMER'S DISEASE

Connor, Daniel 003
A CONTROLLED TRIAL OF EXTENDED-RELEASE BUPROPION IN ADULT ADHD

Cook, Ian 225
DRUG SENSITIVITY IN THE AGING BRAIN AND SUBCLINICAL STRUCTURAL BRAIN DISEASE

Corya, Sara 062
VARYING THE CRITERIA FOR RESPONSE AND REMISSION IN BIPOLAR DEPRESSION

Covell, Nancy 241
DISTRESS WITH MEDICATION SIDE EFFECTS AMONG PERSONS WITH SEVERE MENTAL ILLNESS

Crismon, Lynn 102
TRENDS IN ANTIPSYCHOTIC PRESCRIBING TO CHILDREN AND ADOLESCENTS: 1996 TO 2001

Crook, Thomas 227
EFFECTS OF PNP-12 ON COGNITIVE PERFORMANCE IN AGE-ASSOCIATED MEMORY IMPAIRMENT

D'Souza, R. 186
COMPARATIVE EFFICACY OF SERTRALINE AND VENLAFAXINE-XR IN MAJOR DEPRESSION

D'Souza, R. 201
COMPARATIVE EFFICACY OF SERTRALINE VERSUS VENLAFAXINE-XR IN SEVERE DEPRESSION

Dackis, Charles 022
MODAFINIL IMPROVES COCAINE ABSTINENCE IN COCAINE-DEPENDENCE: A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

***Daley, Tara** 277
DIETARY INTAKE PROFILE OF PATIENTS WITH SCHIZOPHRENIA

David, Daniel 150
IM ZIPRASIDONE IN AGITATED PATIENTS WITH BIPOLAR DIAGNOSES

Davidson, Jonathan 038
A DOUBLE-BLIND COMPARISON OF VENLAFAXINE XR, SERTRALINE, AND PLACEBO IN THE TREATMENT OF PTSD

Davidson, Jonathan 165
ESCITALOPRAM IN THE LONG-TERM TREATMENT OF GENERALIZED ANXIETY DISORDER

Davis, Lori 127
SUBSTANCE USE COMORBIDITY IN MAJOR DEPRESSION: STAR*D PRELIMINARY FINDINGS

Daviss, William 005
CORRELATIONS OF PLASMA DRUG LEVELS AND ADHD RESPONSE IN JUVENILES ON BUPROPION SR

De Luna, Steven 118
SUBJECTIVE VERSUS OBJECTIVE MEASURES OF COMPLIANCE TO A TRANSDERMAL SMOKING CESSATION PROGRAM AMONG PATIENTS ON ANTIPSYCHOTIC MEDICATIONS

De Thomas, Courtney 113
TREATMENT-REFRACTORY CHILDHOOD SCHIZOPHRENIA: CHANGES IN GLUCOSE AND LIPID LEVELS ASSOCIATED WITH ATYPICAL ANTIPSYCHOTICS

DeBattista, Charles 142
A DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL OF C-1073 (MIFEPRISTONE) IN THE TREATMENT OF PSYCHOTIC MAJOR DEPRESSION

**Indicates New Investigator Awardee*

NCDEU 2004 POSTER ABSTRACTS

Presenting Author Index

DeBrota, David 179
SENSITIVITY TO TREATMENT DIFFERENCES IN HIGH ENTRY SCORE VERSUS LOW ENTRY SCORE SUBGROUPS IN DEPRESSION CLINICAL TRIALS

DeBrota, David 284
CORRELATIONS AND FACTOR STRUCTURES WITHIN DATA FROM CONTEMPORANEOUS INTERACTIVE VOICE RESPONSE SYSTEM AND CLINICIAN ADMINISTRATIONS OF THE HAMILTON DEPRESSION RATING SCALE

DeMartinis, Nicholas 040
IMPROVEMENT IN PATIENT-REPORTED FUNCTIONING IN PATIENTS WITH SOCIAL ANXIETY DISORDER TREATED WITH VENLAFAXINE XR, PAROXETINE, OR PLACEBO

DeMartinis, Nicholas 046
SPEED OF ONSET OF PREGABALIN IN GENERALIZED ANXIETY DISORDER

Derogatis, Leonard 163
ABSENCE OF SEXUAL DYSFUNCTION IN PATIENTS WITH MDD TREATED WITH GEPIRONE-ER

Deutschman, Dan 152
HIGH-DOSE ZIPRASIDONE: EFFICACY AND TOLERABILITY IN CLINICAL PRACTICE

***Di Martino, Adriana** 109
SAFETY AND EFFICACY OF METHYLPHENIDATE FOR PERVASIVE DEVELOPMENTAL DISORDERS: AN OPEN LABEL STUDY

Docherty, John 167
CHROMIUM PICOLINATE: ATYPICAL DEPRESSION, CARBOHYDRATE CRAVING AND CLINICAL RESPONSE

Duffy, Farifteh 111
POLYPHARMACY AMONG CHILDREN & ADOLESCENTS TREATED IN ROUTINE PSYCHIATRIC PRACTICE

Dunbar, Geoffrey 126
TC-1734-112 A SELECTIVE NEURONAL NICOTINIC RECEPTOR (NNR) AGONIST IN THE TREATMENT OF COGNITIVE DISORDERS - PHASE 1 RESULTS

***Elhaj, Omar** 066
THE PREVALENCE OF BIPOLAR DISORDER AND COMORBID DISORDERS IN A SAMPLE OF OTTAWA COUNTY JAIL INMATES

Elia, Josephine 098
PANDAS WITH CATATONIA: RESPONSE WITH LORAZEPAM AND PLASMAPHERESIS

Emmanuel, Naresh 034
ESCITALOPRAM IN THE TREATMENT OF MAJOR DEPRESSION WITH COMORBID GAD

Emslie, Graham 160
INCREASED RESPONSE TO PHARMACOTHERAPY IN CHILDHOOD MDD WITH FLEXIBLE DOSE AND EXTENDED TREATMENT: A PRELIMINARY REPORT

Entsuah, Richard 195
COMPLETE REMISSION OF INDIVIDUAL SYMPTOMS AMONG DEPRESSED PATIENTS WITH SEVERE SYMPTOMS AT BASELINE

Eradiri, Okponanabofa 162
STEADY-STATE BIOEQUIVALENCE OF ONCE-DAILY AND TWICE DAILY TABLET FORMULATIONS OF BUPROPION HCL

Evans, Kenneth 148
PRE-RANDOMIZATION WORSENING OF INDIVIDUAL SYMPTOMS OF DEPRESSION: DOES INCREASED ANXIETY PRIOR TO TREATMENT PREDICT PLACEBO RESPONSE?

**Indicates New Investigator Awardee*

***Farabaugh, Amy** 171
THE RELATIONSHIP BETWEEN EARLY CHANGES IN THE HAMD-17 ANXIETY/SOMATIZATION FACTOR ITEMS AND TREATMENT OUTCOME AMONG DEPRESSED OUTPATIENTS

Fava, Maurizio 173
MODAFINIL AS ANTIDEPRESSANT AUGMENTATION THERAPY IN MAJOR DEPRESSIVE DISORDER (MDD)

Fehnel, Sheri 069
ASSESSING THE FUNCTIONAL STATUS OF BIPOLAR PATIENTS

***Feng, Yan** 164
AGE EFFECT ON CITALOPRAM DISPOSITION DEFINED BY A POPULATION PHARMACOKINETIC ANALYSIS

Fleck, David 068
A COMPARISON OF THE EFFICACY AND SAFETY OF QUETIAPINE AND DIVALPROEX SODIUM IN THE TREATMENT OF ACUTE MANIA

Fogarty, Kate 243
REVIEW OF INPATIENT USE OF ANTIPSYCHOTIC DRUGS AT McLEAN HOSPITAL BETWEEN 1989 AND 2002

Fogarty, Kate 270
FIRST SIX MONTHS OF INPATIENT ARIPIPRAZOLE USE AT McLEAN HOSPITAL

Francis, Andrew 249
IM ZIPRASIDONE IN THE PSYCHIATRIC ER: EXPANDED SAMPLE

Freeman, Ellen 256
LUTEAL PHASE VS SYMPTOM-ONSET DOSING WITH ESCITALOPRAM FOR PREMENSTRUAL DYSPHORIC DISORDER: A PRELIMINARY STUDY

Gaynes, Bradley 175
A DIRECT COMPARISON OF DEPRESSED PATIENTS FROM PRIMARY CARE VS. SPECIALTY CARE SETTINGS: PRELIMINARY RESULTS FROM STAR*D

Gelwicks, Steven 177
DOES SMOKING INHIBIT PLACEBO RESPONSE? A RETROSPECTIVE ANALYSIS OF THE EFFECTS OF SMOKING STATUS IN DEPRESSION CLINICAL TRIALS

Gendreau, Michael 281
TREATMENT OF PAIN IN FIBROMYALGIA IS DISTINCT FROM TREATMENT OF MOOD

Gersing, Kenneth 071
USE OF A NATURALISTIC DATABASE TO STUDY PATIENTS AND OUTCOMES IN BIPOLAR DISORDER WITH AND WITHOUT COMORBID SUBSTANCE USE

Gharabawi, Georges 245
INSIGHT IN STABLE PATIENTS WITH SCHIZOPHRENIA RECEIVING LONG-ACTING RISPERIDONE

Gianfrancesco, Frank 214
A COMPREHENSIVE RETROSPECTIVE STUDY OF ASSOCIATIONS BETWEEN DIABETES AND TREATMENT WITH RISPERIDONE, OLANZAPINE, QUETIAPINE, AND CONVENTIONAL ANTIPSYCHOTICS

Ginsberg, Lawrence 072
EXTENDED-RELEASE CARBAMAZEPINE FOR THE TREATMENT OF BIPOLAR DISORDER

Glassman, A.H. 155
NEW SADHART ANALYSIS: POST MI DEPRESSION, A CAUSE OR CONSEQUENCE OF MYOCARDIAL INFARCTION

Gleason, Ondria 110
AN OPEN-LABEL TRIAL OF ESCITALOPRAM FOR MAJOR DEPRESSION IN HEPATITIS C

**Indicates New Investigator Awardee*

NCDEU 2004 POSTER ABSTRACTS

Presenting Author Index

Glick, Ira 228
QUETIAPINE VERSUS HALOPERIDOL DECANOATE FOR LONG-TERM TREATMENT OF SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

Goldberg, Joseph 219
EFFECTS OF MOOD STABILIZER TREATMENT ON MOOD EPISODE RELAPSE AND RECURRENCE IN BIPOLAR DISORDER

Goldstein, Jeffrey 261
TOLERANCE TO SOMNOLENCE WITH QUETIAPINE: PRECLINICAL MECHANISMS AND CLINICAL EVIDENCE

Gonzales-Heydrich, Joseph 096
ZIPRASIDONE IN PEDIATRIC PATIENTS: EFFICACY AND TOLERABILITY

Goodwin, Guy 084
PREVIOUS LITHIUM TREATMENT AS A PREDICTOR OF RESPONSE TO SUBSEQUENT MOOD STABILIZER THERAPY

Graham, Stephen 137
MEMANTINE IS SAFE FOR SHORT- AND LONG-TERM TREATMENT OF DEMENTIA

Greenberg, Irwin 079
COMPARISON OF OLANZAPINE AND LITHIUM TREATMENT GROUPS BASED ON LITHIUM BLOOD LEVELS: A 52-WEEK BIPOLAR RELAPSE PREVENTION STUDY

Gruber, Staci 247
INCREASED AMYGDALAR ACTIVATION AFTER SECRETIN ADMINISTRATION: AN fMRI STUDY

Hamner, Mark 017
A PRELIMINARY CONTROLLED TRIAL OF DIVALPROEX IN PTSD

Harvey, Philip 263
NORMALIZATION OF COGNITIVE FUNCTION WITH LONG-TERM ZIPRASIDONE OR OLANZAPINE

Hellings, Jessica 135
LONG-TERM SAFETY AND ADVERSE EVENTS OF RISPERIDONE IN CHILDREN, ADOLESCENTS AND ADULTS WITH MR/DD

Henderson, David 232
GLUCOSE METABOLISM IN SCHIZOPHRENIA PATIENTS TREATED WITH ATYPICAL ANTIPSYCHOTICS: A FREQUENT SAMPLED INTRAVENOUS GLUCOSE TOLERANCE TEST AND MINIMAL MODEL ANALYSIS

Hindman, David 116
EXPLORATION OF THE EFFECT OF SMOKING CESSATION/REDUCTION ON THE POSITIVE, NEGATIVE AND GENERAL PSYCHIATRIC SYMPTOMS OF PATIENTS ON ANTIPSYCHOTIC MEDICATIONS

Ho, Andrew 036
REAL-TIME IDENTIFICATION OF MISSING DATA IN A FORMS-BASED PROTOCOL MANAGEMENT SYSTEM

***Hoge, Elizabeth** 019
RISPERIDONE FOR THE TREATMENT OF REFRACTORY PANIC, SOCIAL ANXIETY AND GENERALIZED ANXIETY DISORDERS

Horne, Robert 075
DIVALPROEX AS ADJUNCTIVE THERAPY TO ATYPICAL ANTIPSYCHOTIC MEDICATIONS

Horst, Dale 129
EXTENDED USE OF NICOTINE REPLACEMENT THERAPY TO ACHIEVE SMOKING CESSATION IN PERSONS WITH SCHIZOPHRENIA

**Indicates New Investigator Awardee*

***Hunter, Amy** 204
CHANGES IN BRAIN FUNCTION DURING PLACEBO LEAD-IN AND TREATMENT OUTCOME IN CLINICAL TRIALS FOR MAJOR DEPRESSION

Hunziker, Melanie 004
SYMPTOM PROFILES OF CHILDREN AND ADOLESCENTS WITH A DIAGNOSIS OF ADHD, BIPOLAR DISORDER, OR A DEPRESSIVE DISORDER

Husain, Mustafa 168
CORRELATES OF CLINICIAN RATED AND SELF REPORT MEASURES OF DEPRESSION SYMPTOMATOLOGY IN PATIENTS RECEIVING ECT

Iosifescu, Dan 170
FRONTAL EEG PREDICTS CLINICAL RESPONSE TO SSRI TREATMENT IN MDD

Ismail, Saleem 147
CLINICAL COURSE OF CATIE PATIENTS

Jackson, Carlos 120
METHODS FOR EXAMINING RISK OF DIABETES IN PATIENTS TAKING OLANZAPINE COMPARED TO CONVENTIONAL ANTIPSYCHOTIC MEDICATIONS

Jain, Satyam 231
A CHART-REVIEW STUDY OF SRI CONTINUATION TREATMENT VERSUS DISCONTINUATION IN BODY DYSMORPHIC DISORDER

Jain, Shaily 172
PATIENT SATISFACTION WITH PHYSICIAN USE OF A COMPUTER-BASED CLINICAL DECISION SUPPORT SYSTEM(CDSS) DURING TREATMENT FOR A PSYCHIATRIC DISORDER

Jaton, Lisa 058
INITIAL SYMPTOMS OF MANIC RELAPSE

Jaton, Lisa 251
MEDICATION-SPECIFIC CORRELATES OF RELAPSE RISK IN SCHIZOPHRENIA

Kahn, Michael 012
PHARMACOKINETICS OF AN EXTENDED-RELEASE FORMULATION OF MIXED AMPHETAMINE SALTS (MAS XR) IN ADOLESCENTS WITH ADHD

Kalali, Amir 217
THE GRID HAMD: AVAILABILITY OF A NEW STANDARDIZED METHOD FOR THE ASSESSMENT OF DEPRESSION

***Karp, Jordan** 181
BODILY PAIN PREDICTS POOR ANTIDEPRESSANT RESPONSE IN DEPRESSED ELDERLY PRIMARY CARE PATIENTS

Kay, Susan 299
THE USE OF TOPIRAMATE IN PATIENTS WITH EPISODES OF AGGRESSIVE OR IMPULSIVE BEHAVIORS: A REPORT OF SIX CASES

Kelly, Deanna 233
SEXUAL FUNCTION AND PROLACTIN LEVELS: A RANDOMIZED DOUBLE-BLIND 12-WEEK STUDY OF QUETIAPINE, RISPERIDONE OR FLUPHENAZINE

Kemner, Jason 006
SAFETY AND EFFECTIVENESS OF OROS MPH AND ATOMOXETINE

Ketter, Terence 024
SUSTAINED REMISSION/EUTHYMIA WITH QUETIAPINE MONOTHERAPY FOR BIPOLAR MANIA

**Indicates New Investigator Awardee*

NCDEU 2004 POSTER ABSTRACTS

Presenting Author Index

Khan, Arif 183
RESEARCH DESIGN FEATURES AND PATIENT CHARACTERISTICS RELATED TO ANTIDEPRESSANT CLINICAL TRIAL OUTCOME

Khan, Sajjad 234
PREDOMINANCE OF PSYCHIATRIC-BASED REASONS FOR ANTIPSYCHOTIC TREATMENT DISCONTINUATION

Klee, Brian 023
RESPIRATORY AND AUTONOMIC PANIC DISORDER SUBTYPES: CLINICAL CORRELATES AND RESPONSE TO ALPRAZOLAM-XR

Kline, Neal 025
PARTIAL REPORTING OF THE CLINICAL GLOBAL IMPRESSION-IMPROVEMENT SCALE IN POSTTRAUMATIC STRESS DISORDER CLINICAL TRIALS: ARE PTSD CGI-IS MIA?

Knapp, Rebecca 295
RACIAL DIFFERENCES IN RESPONSE TO ECT: A COMPARISON OF AFRICAN-AMERICAN VERSUS CAUCASIAN POPULATIONS

Kobak, Kenneth 185
A COMPARISON OF FACE-TO-FACE AND REMOTE ADMINISTRATION OF THE HAMILTON DEPRESSION RATING SCALE VIA VIDEOCONFERENCING

Kogan, Jane 077
PAROXETINE AND SUICIDALITY IN A HIGH-RISK POPULATION

Kolts, Russell 174
RELATIVE SENSITIVITY OF THE MONTGOMERY-ASBERG DEPRESSION RATING SCALE, THE HAMILTON DEPRESSION RATING SCALE, AND THE CLINICAL GLOBAL IMPRESSIONS RATING SCALE IN ANTIDEPRESSANT CLINICAL TRIALS

Koran, Lorrin 210
ESCITALOPRAM IN THE TREATMENT OF COMPULSIVE BUYING DISORDER AND KLEPTOMANIA

Korndorfer, Sergio 100
A COMPARISON OF DIVALPROEX, GABAPENTIN AND OXCARBAZEPINE IN AGGRESSIVE YOUTH

Kornstein, Susan 187
MAINTENANCE TREATMENT WITH ESCITALOPRAM PREVENTS RECURRENCE OF DEPRESSIVE EPISODES

Kostic, Dusan 208
FLEXIBLE DOSE ARIPIPRAZOLE IN PSYCHOSIS OF ALZHEIMER'S DEMENTIA (AD)

Krishnan, Anupama 268
THE BURDEN OF DEPRESSION IN PATIENTS WITH BIPOLAR DISORDER

L'Italien, Gilbert 280
COMPARATIVE OVERALL EFFECTIVENESS OF SCHIZOPHRENIA PATIENTS TREATED WITH ATYPICAL ANTIPSYCHOTICS OLANZAPINE VERSUS ARIPIPRAZOLE

Lavretsky, Helen 128
ANTIDEPRESSANT EXPOSURE MAY PROTECT AGAINST DECREMENT IN FRONTAL GRAY MATTER VOLUMES IN GERIATRIC DEPRESSION

Leaderer, Megan 220
ZIPRASIDONE VERSUS OLANZAPINE: CONTRASTS IN CHD RISK

Lehman, Robert 115
A STUDY OF OXCARBAZEPINE IN THE TREATMENT OF DISRUPTIVE BEHAVIORS OF CHILDREN AND ADOLESCENTS

Leventer, Steven 112
DEXTOFISOPAM: A NOVEL HOMOPHTHALAZINE WITH POTENTIAL FOR TREATMENT OF STRESS-RELATED DISORDERS

Levine, Louise 021
EFFECTS OF TREATMENT WITH LY354740, LORAZEPAM, OR PLACEBO IN PATIENTS WITH A PRIMARY DIAGNOSIS OFGENERALIZED ANXIETY DISORDER

Lightfoot, Jeffrey 257
PILOT EVALUATION OF ATOMOXATINE AUGMENTATION OF CLOZAPINE AS A TREATMENT FOR THE COGNITIVE SYMPTOMS OF SCHIZOPHRENIA

Loebel, Antony 230
LONG-TERM COGNITIVE IMPROVEMENT IN PATIENTS SWITCHED TO ZIPRASIDONE

Loescher, Amy 189
RESULTS FROM THE ARISE-RD (AUGMENTATION WITH RISPERIDONE IN RESISTANT DEPRESSION) TRIAL

Loney, Jan 002
MIDLIFE OUTCOMES OF 100 ADHD BOYS: PREDICTION BY ASPECTS OF TREATMENT WITH METHYLPHENIDATE

Macfadden, Wayne 053
ANTI-ANXIETY EFFECTS ANALYSIS OF QUETIAPINE IN BIPOLAR DEPRESSION

Macfadden, Wayne 082
DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF QUETIAPINE IN BIPOLAR DEPRESSION

Mallinckrodt, Craig 205
COMPARING METHODOLOGIES FOR ASSESSING ONSET OF ACTION IN NEUROPSYCHIATRIC CLINICAL TRIALS

Marin, Humberto 242
EFFECT OF ANTIPSYCHOTIC CHANGE ON WEIGHT IN MINORITIES

Martynov, Oleg 166
HEPATIC MONITORING IN CLINICAL TRIALS: A CASE STUDY

Masand, Prakash 027
RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND TRIAL OF PAROXETINE CONTROLLED RELEASE IN IRRITABLE BOWEL SYNDROME

Masand, Prakash 191
AN OPEN-LABEL, RATER BLINDED STUDY OF ARIPIPRAZOLE AS AN AUGMENTATION AGENT IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

Mattes, Jeffrey 301
OXCARBAZEPINE IN PATIENTS WITH IMPULSIVE AGGRESSION

Matthews, John 297
USE OF GALANTAMINE HBr IN ELECTROCONVULSIVE THERAPY

McGarvey, Elizabeth 123
RELIABILITY ANALYSIS AND CONSTRUCT VALIDITY OF THE CHANGES IN SEXUAL FUNCTIONING QUESTIONNAIRE (CSFG) SHORT FORM FOR WOMEN AND MEN

McIntyre, Roger 288
EFFICACY OF QUETIAPINE IN MANIA ASSOCIATED WITH BIPOLAR DISORDER

McQuade, Robert
ARIPIPRAZOLE VERSUS PLACEBO IN PATIENTS WITH ACUTE MANIC OR MIXED EPISODE 264

NCDEU 2004 POSTER ABSTRACTS

Presenting Author Index

Mintzer, Jacobo 130
GALANTAMINE IN THE TREATMENT OF DEMENTIA IN HISPANIC PATIENTS:AN EFFECTIVENESS MULTICENTER OPEN LABEL STUDY

Mintzer, Jacobo 138
THE INFLUENCE OF ETHNIC BACKGROUND AND CARDIOVASCULAR RISK FACTORS ON COGNITIVE ASSESSMENT OF A LONGITUDINAL COMMUNITY BASED SAMPLE

Mischoulon, David 193
DOUBLE-BLIND DOSE-FINDING STUDY OF DOCOSAHEXANOIC ACID (DHA) IN MAJOR DEPRESSIVE DISORDER

Moreno, Francisco 081
CARNITINE LEVELS IN PSYCHIATRIC PATIENTS TREATED CHRONICALLY WITH VALPROIC ACID

Moreno, Francisco 287
SAFETY, TOLERABILITY, AND EFFICACY OF PSILOCYBIN IN TREATMENT REFRACTORY OCD

Morris, Chad 083
CARE SATISFACTION, HOPE, AND LIFE FUNCTIONING AMONG ADULTS WITH BIPOLAR DISORDER: DATA FROM THE FIRST 1,000 STEP-BD PARTICIPANTS

Mundt, James 180
ASSESSING DEPRESSION: HOW MUCH TIME AND EFFORT DOES IT TAKE VIA INTERACTIVE VOICE RESPONSE (IVR)?

Musgnung, Jeff 182
COMPLETE SOMATIC SYMPTOM RESOLUTION WITH VENLAFAXINE OR SSRIS

Musgnung, Jeff 197
DEPRESSION REMISSION RATES AMONG PATIENTS TREATED WITH VENLAFAXINE XR OR SSRIS USING TREATMENT ALGORITHMS

Myrick, Hugh 015
MODAFINIL AS POTENTIAL TREATMENT FOR COCAINE DEPENDENCE

Negron, Arnaldo 255
DIVALPROEX SODIUM EXTENDED RELEASE FOR ACUTE TREATMENT OF SCHIZOPHRENIA: A RETROSPECTIVE CHART REVIEW"

Nelligan, Julie 199
ANTIDEPRESSANT USE IN VETERANS WITH HEPATITIS C

Niazi, Shehzad 049
DOUBLE BLIND PLACEBO CONTROLLED STUDY OF GENDER-BASED VARIABILITY IN NEURO-IMMUNOLOGICAL, NEURO-ENDOCRINE MEASURES WITH SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI) TREATMENT OF POSTTRAUMATIC STRESS DISORDER (PTSD).

Niculescu, Alexander 064
PHENOCHIPPING OF PSYCHOTIC DISORDERS: A NOVEL APPROACH FOR DECONSTRUCTING AND QUANTITATING PSYCHIATRIC PHENOTYPES

Nierenberg, Andrew 184
STAR*D SAFETY MONITORING: LESSONS FROM A LARGE HYBRID STUDY OF DEPRESSION

Nihalani, Nikhil 048
TIAGABINE IN GAD PATIENTS WHO WERE PARTIAL RESPONDERS TO SSRI THERAPY: AN OPEN-LABEL STUDY

Nihalani, Nikhil 207
ADJUNCT MODAFINIL REDUCES ANTIDEPRESSANT-INDUCED SEDATION IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Ninan, Philip 031
TIAGABINE IMPROVES SYMPTOMS OF SOCIAL ANXIETY DISORDER: AN OPEN- LABEL STUDY

O'Hara, Ruth 190
APOE4 ALLELE INFLUENCES ANTIDEPRESSANTS' COGNITIVE EFFECTS IN THE ELDERLY

Ohlsen, Ruth 218
DIFFERENTIAL EFFECTS OF ANTIPSYCHOTIC MEDICATIONS ON OVERWEIGHT PEOPLE WITH SEVERE MENTAL ILLNESS IN A PSYCHOSOCIAL WEIGHT LOSS PROGRAMME

Olfson, Mark 146
NATIONAL PATTERNS IN THE CONTINUITY OF ANTIDEPRESSANT TREATMENT FOR DEPRESSION

Olin, Jason 141
FUNCTIONAL AND BEHAVIORAL EFFECTS OF MEMANTINE IN ALZHEIMER'S DISEASE

Olin, Jason 151
RESPONSE TO MEMANTINE TREATMENT BASED ON MULTIPLE DEFINITIONS OF RESPONDERS

Opler, Mark 292
THE EFFICACY OF QUETIAPINE IN THE TREATMENT OF DELUSIONAL DISORDER

Oren, Dan 055
ARIPIPRAZOLE FOR RELAPSE PREVENTION IN A 26-WEEK PLACEBO-CONTROLLED TRIAL IN BIPOLAR DISORDER

***Ostacher, Michael** 085
CHARACTERISTICS OF PATIENTS TREATED WITH GABAPENTIN REFERRED TO A BIPOLAR SPECIALTY CLINIC

Pandina, Gahan 238
THE RELATIONSHIP BETWEEN COGNITIVE MEASURES AND FUNCTIONAL OUTCOMES IN SCHIZOPHRENIA

Papakostas, George 014
AN ACADEMIC SPECIALTY CLINIC-BASED COMPARISON OF NEXT-STEP SWITCHING VERSUS AUGMENTATION STRATEGIES IN OUTPATIENTS WITH MAJOR DEPRESSIVE DISORDER RESISTANT TO A SINGLE ANTIDEPRESSANT TRIAL

***Patel, Nick** 240
ADHERENCE TO CLOZAPINE: EFFECTS OF REDUCED FREQUENCY OF HEMATOLOGIC MONITORING

Pathak, Sanjeev 290
PSYCHOTROPIC UTILIZATION AND CLINICAL PRESENTATION OF HOSPITALIZED VERY-YOUNG CHILDREN

Patkar, Ashwin 042
PREDICTORS OF RESPONSE TO A PLACEBO-CONTROLLED, DOUBLE-BLIND TRIAL OF PAROXETINE CONTROLLED RELEASE IN FIBROMYALGIA

***Payne, Jennifer** 235
RILUZOLE: AN INVESTIGATION OF THE ANTIDEPRESSANT EFFICACY OF AN ANTIGLUTAMATERGIC AGENT WITH NEUROTROPHIC PROPERTIES

Perlis, Roy 028
ATYPICAL ANTIPSYCHOTICS IN THE TREATMENT OF MANIA: A META-ANALYSIS OF RANDOMIZED CONTROLLED MONOTHERAPY TRIALS

Perlis, Roy 285
ATYPICAL ANTIPSYCHOTICS IN THE TREATMENT OF MANIA: A META-ANALYSIS OF RANDOMIZED, PLACEBO-CONTROLLED COMBINATION THERAPY TRIALS

**Indicates New Investigator Awardee*

NCDEU 2004 POSTER ABSTRACTS

Presenting Author Index

Pesa, Jacqueline 091
WORK LOSS ASSOCIATED WITH BIPOLAR DISORDER

Petrie, William 076
RISPERIDONE VERSUS OLANZAPINE AS ADJUNCTIVE THERAPY IN THE TREATMENT OF PATIENTS WITH BIPOLAR DISORDER WHO ARE RECEIVING A PRIMARY THYMOLEPTIC AGENT

Phillips, Katharine 229
PHARMACOTHERAPY RECEIVED BY INDIVIDUALS WITH BODY DYSMORPHIC DISORDER

Pitts, Cornelius 196
TOLERABILITY OF CONTROLLED RELEASE PAROXETINE IN PATIENTS PREVIOUSLY INTOLERANT TO SSRI/SNRI THERAPY

Pollack, Mark 041
EFFICACY OF PREGABALIN IN CLINICALLY RELEVANT SUBTYPES OF GAD

Pomara, Nunzio 132
ENHANCED DELAYED RECALL OF PRE-DRUG WORD LIST FOLLOWING ACUTE LORAZEPAM AND TRIHEXYPHENIDYL ADMINISTRATION IN HEALTHY ELDERLY

Pomara, Nunzio 136
MEMANTINE MONOTHERAPY IS EFFECTIVE AND SAFE FOR THE TREATMENT OF MILD TO MODERATE ALZHEIMER'S DISEASE: A RANDOMIZED CONTROLLED TRIAL

Posternak, Michael 158
ARE THERE DIFFERENCES BETWEEN DEPRESSED PSYCHIATRIC OUTPATIENTS WHO WOULD AND WOULD NOT QUALIFY FOR AN ANTIDEPRESSANT EFFICACY TRIAL?

Potkin, Steven 056
ZIPRASIDONE IN BIPOLAR MANIA: EFFICACY ACROSS PATIENT SUBGROUPS

Potts, Alison 097
OLANZAPINE VERSUS RISPERIDONE IN THE TREATMENT OF BIPOLAR I DISORDER: DETERMINANTS OF CHANGE IN SEVERITY OF BIPOLAR ILLNESS RATINGS

Preskorn, Sheldon 202
THE POTENTIAL FOR CLINICALLY SIGNIFICANT DRUG-DRUG INTERACTIONS IN PATIENTS RECEIVING CYP 2D6 MODEL SUBSTRATE/DRUGS AND FLUOXETINE/PAROXETINE OR SERTRALINE

Quiroz, J.A. 080
RILUZOLE: AN INVESTIGATION OF THE ANTIDEPRESSANT EFFICACY OF AN ANTIGLUTAMATERGIC AGENT WITH NEUROTROPHIC PROPERTIES IN BIPOLAR DEPRESSION

Quitkin, Frederic 192
ASSESSMENT OF ANTIDEPRESSANT EFFECTIVENESS IN THREE SUCCESSIVE TRIALS

Rajnish, Mago 149
A SURVEY OF CLINICIANS REGARDING THE TREATMENT OF ALZHEIMER'S DISEASE IN 2003

***Ramaswamy, Sriram** 033
FACTORS ASSOCIATED WITH MISSED FIRST APPOINTMENTS IN SUBJECTS VOLUNTEERING TO PARTICIPATE IN A CLINICAL TRIAL OF POSTTRAUMATIC STRESS DISORDER

Rapaport, Mark 203
ESCITALOPRAM IMPROVES SOMATIC SYMPTOMS OF DEPRESSION

Reilly, Noreen 087
AN INTERACTIVE COMPUTER INTERVIEW FOR MANIA TO ENHANCE HUMAN RATER PERFORMANCE

Rodriguez, Stephen 253
MANUAL-GUIDED USE OF LONG-ACTING RISPERIDONE IN COMMUNITY-BASED SETTINGS

Rosenberg, Russell 254
EFFICACY AND TOLERABILITY OF INDIPLON-IR FOR CHRONIC INSOMNIA: RESULTS USING BEDTIME AND MIDDLE OF THE NIGHT DOSING STRATEGIES

Rosenberg, Leon 144
LET THE HAMILTON RATING SCALE FOR DEPRESSION SPEAK FOR ITSELF

Rosenberg, Russell 252
SAFETY, TOLERABILITY, AND PATIENT FUNCTIONAL STATUS WITH LONG-TERM MODAFINIL IN CHRONIC SHIFT WORK SLEEP DISORDER

Roth, Thomas 267
MODAFINIL FOR THE TREATMENT OF EXCESSIVE SLEEPINESS ASSOCIATED WITH CHRONIC SHIFT WORK SLEEP DISORDER

***Ruiz-Mellott, Katherine** 131
ETHNIC VARIATIONS IN ANTIDEPRESSANT RESPONSE RATE IN SUBJECTS WITH MAJOR DEPRESSION AND CO-OCCURRING ALCOHOL USE DISORDER: THE ROLE OF SEROTONIN TRANSPORTER POLYMORPHISM

Rupnow, Marcia 266
IMPROVEMENT IN GLOBAL FUNCTIONING IN BIPOLAR PATIENTS: RESULTS FROM AN OPEN-LABEL, RISPERIDONE STUDY

Rush, John 194
A ONE-YEAR LONGITUDINAL STUDY OF VNS THERAPY IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION

Sachs, Gary 279
THE LONG-TERM IMPACT OF MOOD STABILIZERS ON BODY WEIGHT

Safer, Daniel 119
A COMPARISON OF RISPERIDONE-INDUCED WEIGHT GAIN ACROSS THE AGE SPAN

Sajatovic, Martha 289
RESPONSE TO MOOD STABILIZERS IN OLDER PATIENTS WITH BIPOLAR I DISORDER

Salloum, Ihsan 125
BIPOLAR DEPRESSION AND UNIPOLAR DEPRESSION RESPONSE TO TREATMENT IN THE CONTEXT OF COMORBID ALCOHOLISM

Salmán, Ester 275
REAL-TIME DIGITAL DATA CAPTURE (DDC): A CLINICAL TRIAL TOOL FOR ENHANCING DATA QUALITY AND PROMOTING CLINICAL RATING RELIABILITY

Sanchez, Robert 007
ADHERENCE MEASURES OF PSYCHOSTIMULANTS USED IN THE TREATMENT OF ADHD IN CHILDREN AND ADOLESCENTS

Sarkis, Elias 008
SAFETY PROFILE OF BUPROPION SR IN CHILDREN: A RETROSPECTIVE CHART REVIEW

Schaffer, Ayal 070
DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT STUDY OF MEXILETINE FOR MANIA OR HYPOMANIA

Scharf, Martin 106
EFFICACY OF INDIPLON-MR IN INDUCING AND MAINTAINING SLEEP IN PATIENTS WITH CHRONIC SLEEP MAINTENANCE INSOMNIA

**Indicates New Investigator Awardee*

NCDEU 2004 POSTER ABSTRACTS

Presenting Author Index

Schiller, Mark 221
REFERENCED-EEG IN THE TREATMENT OF EATING DISORDERS

Schneck, Christopher 095
PHENOMENOLOGY OF RAPID CYCLING BIPOLAR DISORDER: DATA FROM THE FIRST 500 PARTICIPANTS IN THE SYSTEMATIC TREATMENT ENHANCEMENT PROGRAM FOR BIPOLAR DISORDER

***Schvartz, Inika** 121
THE IMPACT OF CLOZAPINE ON AGGRESSIVE BEHAVIOR AMONG CHILDREN AND ADOLESCENTS WITH SCHIZOPHRENIA

Sharma, Tonmoy 246
COGNITIVE EFFECTS OF ZIPRASIDONE IN FIRST EPISODE PSYCHOSIS: AN fMRI STUDY

Shelton, Richard 291
SERTRALINE AND VENLAFAXINE IN MAJOR DEPRESSION

Shults, Justine 060
FLUOXETINE MONOTHERAPY OF BIPOLAR TYPE II MAJOR DEPRESSION - LACK OF MANIC INDUCTION

Silkey, Beryl 200
MULTI-SITE STUDY OF OUTPATIENT MULTIPLE MEDICATION USE IN RELATION TO AGE AND ANTIDEPRESSANT DRUG USE

Sills, Terrence 153
AN ITEM RESPONSE THEORY ANALYSIS OF THE HAMILTON DEPRESSION RATING SCALE: GENDER DIFFERENCES IN MEASURING DEPRESSION SEVERITY

Silva, Raul 016
COMPARISON OF LONG-ACTING METHYLPHENIDATE FORMULATIONS IN CHILDREN WITH ADHD: POOLED ANALYSIS OF 2 RANDOMIZED, PLACEBO-CONTROLLED STUDIES

Simon, Naomi 043
PREGABALIN IN GENERALIZED ANXIETY DISORDER: INFLUENCE OF DEPRESSIVE SYMPTOMS ON ANXIOLYTIC EFFICACY

Simpson, George 237
ZIPRASIDONE: LONG-TERM POST-SWITCH EFFICACY IN SCHIZOPHRENIA

***Singh, Jaskaran** 088
PRAMIPEXOLE FOR BIPOLAR II DEPRESSION

Sir, A. 188
COMPARATIVE EFFICACY OF SERTRALINE VERSUS VENLAFAXINE-XR IN ANXIOUS-DEPRESSION

Sir, A. 272
TOLERABILITY AND DISCONTINUATION EFFECTS FOR SERTRALINE VERSUS VENLAFAXINE-XR IN DEPRESSION

Skaer, Tracy 209
ANTIDEPRESSANT TRENDS AMONG CHILDREN AND ADOLESCENTS DIAGNOSED WITH DEPRESSION: 1990-2001

Smelson, David 001
A COMMUNITY LINKAGE INTERVENTION TO TRANSITION INDIVIDUALS WITH A CO-OCCURING SUBSTANCE ABUSE AND PSYCHIATRIC DISORDER FROM ACUTE PSYCHIATRY TO OUTPATIENT CARE

Smith, Michael 133
SMOKING REDUCTION IMPACT ON CYP1A2 ACTIVITY IN A GROUP OF PATIENTS RECEIVING ANTIPSYCHOTICS

***Snyderman, Steven** 029
ZIPRASIDONE FOR TREATMENT-REFRACTORY GENERALIZED ANXIETY DISORDER: AN OPEN-LABEL, FLEXIBLE-DOSE PILOT STUDY

**Indicates New Investigator Awardee*

Soares, Claudio 198
IMPACT OF ESCITALOPRAM VERSUS NORETHINDRONE ACETATE AND ETHINYL ESTRADIOL ON DEPRESSION, VASOMOTOR SYMPTOMS, AND QUALITY OF LIFE IN PERI AND POSTMENOPAUSAL WOMEN: A RANDOMIZED TRIAL

Soldani, Federico 090
RELATION OF FUNDING-SOURCE, METHODOLOGICAL QUALITY AND STUDY-OUTCOME IN BIPOLAR DISORDER DRUGS REPORTS

Sonnenberg, John 212
A PRE AND POST ANALYSIS OF CLOZAPINE BLOOD LEVELS AND CLINICAL GLOBAL IMPRESSIONS FOR SUBJECTS SWITCHED FROM NOVARTIS BRAND CLOZARIL TO IVAX BRAND CLOZAPINE

Spencer, Thomas 010
A COHORT ANALYSIS OF MEASURED GROWTH PARAMETERS IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER RECEIVING MIXED AMPHETAMINE SALTS (MAS XR) FOR 24 MONTHS

Spencer, Thomas 018
EFFICACY OF DEXMETHYLPHENIDATE EXTENDED-RELEASE CAPSULES IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Stahl, Stephen 050
ATYPICAL ANTIPSYCHOTICS AND RECEPTOR BINDING: ENHANCING COGNITION AND MOOD

Stassen, Hans 051
A MOLECULAR-GENETIC APPROACH TO MODELING PSYCHOTROPIC DRUG RESPONSE

Stirewalt, Edna 244
QUETIAPINE FOR AGITATION AND AGGRESSION IN BIPOLAR MANIA

Stroble, Anna 278
DOUBLE-BLIND COMPARISON OF A FIXED DOSE OF ESCITALOPRAM (10 MG/DAY) AND AN OPTIMAL DOSING REGIMEN OF SERTRALINE (50-200 MG/DAY) IN DEPRESSED PATIENTS

Swanson, James 009
MODAFINIL AS THERAPY FOR ADHD IN CHILDREN: AN 8-WEEK, OPEN-LABEL STUDY

Swope, Gia 092
AN OPEN LABEL STUDY OF LAMOTRIGINE IN ADOLESCENTS WITH BIPOLAR MOOD DISORDER

Targum, Steven 035
QUETIAPINE REDUCES PERSISTENT ANXIETY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Targum, Steven 293
RATER EXPERIENCE IN CNS CLINICAL TRIALS

Taylor, Charles 250
MUTATION STUDIES OF PREGABALIN BINDING AND PHARMACOLOGY IN VIVO AT ALPHA2-DELTA PROTEINS

Terrence, Early 157
SEVOFLURANE BURST SUPPRESSION THERAPY FOR TREATMENT-RESISTANT DEPRESSION

Toalson, Pat 061
EARLY WEIGHT GAIN AS A PREDICTOR OF SUBSTANTIAL WEIGHT: RESULTS FROM SEVEN STUDIES OF OLANZAPINE FOR THE TREATMENT OF BIPOLAR DISORDER

Tohen, Mauricio 067
TIME IN EUTHYMIA FOR BIPOLAR PATIENTS RECEIVING OLANZAPINE OR LITHIUM MAINTENANCE TREATMENT

Trapp, George 134
MEASUREMENT OF OLFACTORY ABILITY: ODOR IDENTIFICATION IS NOT EQUIVALENT TO OLFACTORY THRESHOLD

**Indicates New Investigator Awardee*

NCDEU 2004 POSTER ABSTRACTS

Presenting Author Index

Trivedi, Madhukar 213
IMPLEMENTATION OF A COMPUTERIZED TREATMENT ALGORITHM FOR DEPRESSION IN REAL WORLD PRACTICE

***Truman, Christine** 099
ARE ANTIDEPRESSANTS ASSOCIATED WITH SWITCHING FROM MAJOR DEPRESSION TO MANIA IN PATIENTS WITH BIPOLAR I DISORDER?

Turkoz, Ibrahim 215
IMPROVEMENT IN QUALITY OF LIFE WITH RISPERIDONE AUGMENTATION IN TREATMENT-RESISTANT DEPRESSION

Uhlenhuth, E. 037
ABRUPT DISCONTINUATION OF ALPRAZOLAM IN PANIC PATIENTS: ANXIETY DURING THE NEXT 24 HOURS

Urioste, Ronald 248
THE GAIN ACCEPTANCE APPROACH: A NOVEL PSYCHOSOCIAL APPROACH TO SUPPORTING PATIENT ACCEPTANCE OF A LONG-ACTING INJECTABLE ANTIPSYCHOTIC

Van Brunt, David 236
DETERMING OPTIMUM MEDICATION IN SCHIZOPHRENIC PATIENTS: DEVELOPMENT OF A STATISTICAL MODEL

Viguera, Adele 276
ANTICONVULSANTS IN PREGNANCY AND LACTATION: DIFFERENCES IN ATTITUDES AND PRACTICE PATTERNS AMONG NEUROLOGISTS AND PSYCHIATRISTS

Votolato, Nicholas 104
ACUTE WEIGHT GAIN WITH COMBINATION DIVALPROEX SODIUM AND OLANZAPINE IN CHILDREN AND ADOLESCENT INPATIENTS AT A UNIVERSITY HOSPITAL

Votolato, Nick 286
PLACEBO-LEVEL EPS AND AKATHISIA DURING QUETIAPINE TREATMENT FOR MANIA

Wagner, Karen Dineen 117
EFFICACY OF SERTRALINE IN AN ANXIOUS SUBGROUP OF YOUTHS WITH MAJOR DEPRESSION

Wan, George 011
ADHD SYMPTOM RESPONSE AND REMISSION AS A FUNCTION OF STIMULANT THERAPY DOSAGE

Warrington, Lewis 059
EFFICACY AND SAFETY OF ZIPRASIDONE IN BIPOLAR DISORDER: LONG-TERM DATA

***Waxmonsky, James** 020
THE IMPACT OF AFFECTIVE SYMPTOMATOLOGY ON THE MULTIMODAL TREATMENT OF PEDIATRIC ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

Weiden, Peter 216
COURSE OF WEIGHT & METABOLIC BENEFITS 1 YEAR AFTER SWITCHING TO ZIPRASIDONE

Weiler, Richard 101
EXTENDED-RELEASE CARBAMAZEPINE MONOTHERAPY FOR ACUTE MANIA AND MIXED SYMPTOMS ASSOCIATED WITH BIPOLAR DISORDER

Weisler, Richard 073
ADJUNCTIVE ZIPRASIDONE IN BIPOLAR MANIA: LONG-TERM DATA

Weissman, Ellen 259
IMPACT OF RISPERIDONE TABLET-SPLITTING ON CLINICAL OUTCOMES AND MEDICATION ADHERENCE

Wesnes, Keith 013
THE EFFECTS OF GINKGO BILOBA ON MEMORY IN HEALTHY MIDDLE-AGED VOLUNTEERS

**Indicates New Investigator Awardee*

Wesnes, Keith 140
EFFECTS OF GALANTAMINE AND DONEPEZIL ON ATTENTION IN PATIENTS WITH MODERATE-TO-SEVERE ALZHEIMER'S DISEASE

Wesnes, Keith 283
UNDERSTANDING AND ADDRESSING REGULATORY QUESTIONS IN THE USE OF TECHNOLOGY SOLUTIONS TO COLLECT PATIENT REPORTED OUTCOMES DATA

Wilk, Joshua 039
ARE ANXIETY DISORDERS UNDERDIAGNOSED AND UNDERTREATED IN ROUTINE PSYCHIATRIC PRACTICE?

Wilkinson, Candace 063
SERUM LEVEL CHANGES ASSOCIATED WITH SWITCHING PSYCHIATRIC PATIENTS FROM A DELAYED-RELEASE TO AN EXTENDED-RELEASE FORMULATION OF DIVALPROEX SODIUM

Williams, Emily 114
GROUP EDUCATION IN VETERANS WITH HEPATITIS C

Wisniewski, Stephen 211
ESTABLISHING TECHNOLOGY-BASED COMMUNICATIONS IN THE SEQUENCED TREATMENT ALTERNATIVES TO RELIEVE DEPRESSION (STAR*D) PROJECT

Worthington, John 026
ARIPRAZOLE AS AN AUGMENTOR OF SSRIS IN MOOD AND ANXIETY DISORDER PATIENTS

Worthington, John 045
ATOMOXETINE AUGMENTATION FOR REFRACTORY ANXIETY DISORDERS

Wu, Eric 052
DRUG TREATMENT PATTERNS OF BIPOLAR DISORDER AND ASSOCIATED COSTS

Wunderlich, Glen 273
A VALIDATION STUDY OF THE SEXUAL INTEREST AND DESIRE INVENTORY (SIDI)

Young, R.C. 057
DONEPEZIL IN BIPOLAR DISORDERS WITH COGNITIVE IMPAIRMENT/ DEMENTIA

Zemlan, Frank 265
MULTICENTER STUDY OF THE SAFETY AND EFFICACY OF THE MELATONIN AGONIST LY156735 IN PRIMARY INSOMNIA

Zimbroff, Dan 169
ESCITALOPRAM TREATMENT OF SSRI NON-RESPONDERS CAN LEAD TO REMISSION IN PATIENTS WHO FAIL INITIAL SSRI THERAPY

Zimmerman, Mark 161
A REVIEW OF SSRI COMPARISON TRIALS

Zimmerman, Mark 274
USING A SELF-REPORT DEPRESSION SCALE TO IDENTIFY REMISSION IN DEPRESSED OUTPATIENTS

Zito, Julie 206
COMPARATIVE PREVALENCE OF PSYCHOTROPIC MEDICATION FOR YOUTH: MEDICAID VERSUS PRIVATE INSURANCE