Identifying Common Targets Across Brain Diseases – Implications for Treatment Development and Delivery
PANEL OVERVIEW:
THE CLINICAL IMPLICATIONS OF CHRONIC HYponATREMIA IN MENTAL HEALTH AND AGING: NEW FINDINGS

Richard Josiassen¹, PhD, Joseph Verbalis², MD, Arthur Siegel³, MD, Myron Miller⁴, MD

¹Drexel University College of Medicine; ²Georgetown University Medical Center,
³McLean Hospital; ⁴Johns Hopkins Bayview Medical Center

Chronic hyponatremia (serum sodium concentration [Na+] < 136 mEq/L) is a common electrolyte disorder observed in patients with mental illnesses. The early manifestations (e.g., headache, nausea, lethargy, restlessness, and confusion) are nonspecific and often mistaken for aspects of the primary psychiatric disorder itself. As a result, chronic hyponatremia (CH) often goes unrecognized and unmanaged until the patient becomes severely agitated or has a seizure secondary to a precipitous drop in serum [Na+]. Fluid restriction has been the treatment of choice, but the benefits are often undermined by poor patient compliance. When fluid restriction fails to normalize serum [Na+] most psychiatrists do not initiate further treatment (e.g., sodium supplementation, loop diuretics, demeclocycline) due to the prevailing view that mild to moderate CH is benign.

However, mild CH is not benign. New findings show that mild CH is associated with (1) gait, motor, balance, and attentional impairment contributing to an increased rate of falls, (2) decreased bone mineral density and increasing bone fragility, and (3) increased risk for subsequent development of “acute” hyponatremia. Thus, if not effectively treated, CH may have a negative impact on the long-term quality of life. In light of these findings, the recent demonstrations that vasopressin antagonists (known as “vaptans”) effectively treat hyponatremia is an important development.

This symposium will review recent advances into the causes and treatment of CH in psychiatric and aging populations. The session will begin with an update on the diagnosis of hyponatremia and the increased morbidity and mortality associated with CH. Next, gait, balance, and motor disturbance will be reviewed. Next, aging and hyponatremia will be discussed. Finally, the efficacy of vasopressin receptor antagonists will be discussed.

As a result of this panel, the participants will be able to (1) Define the prevalence and clinical consequences of hyponatremia in mental disorders and aging; (2) More fully appreciate issues related to the proper rate of correction of hyponatremia; and, (3) Describe current etiological models of hyponatremia in mental health and aging.

Learning Objectives:
- Define the prevalence and clinical consequences of hyponatremia in mental disorders and aging
- Appreciate issues related to the diagnosis and proper rate of correction of hyponatremia
- Describe current etiological models of hyponatremia in mental health and aging

PANEL: HYponATREMIA – AN OLD DISORDER WITH NEW FINDINGS

Joseph Verbalis, MD
Georgetown University Medical Center

There is a high prevalence of chronic hyponatremia, defined as serum Na < 135 mmol/L, in the aging population. Hyponatremia in the elderly is frequently due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) as a result of age-related disruption of the inhibitory component of brain osmoregulatory mechanisms. Although this condition is often asymptomatic, recent reports have shown adverse effects of hyponatremia on cognitive function and gait stability leading to an increased risk of falling, which represents a risk factor for fractures. Recent research has indicated that chronic hyponatremia is associated with gait disturbances, increased falls, and increased fractures in humans. We have found that chronic hyponatremia also causes increased bone resorption and reduced bone mineral density in both young and aged rats. Analysis of data from the Third National Health and Nutrition Examination Survey (NHANES III) by multiple linear regression models demonstrated that among hyponatremic participants, serum [Na+] explained 14.7% of the variation in total hip BMD; for every one mmol/L decrease in serum [Na+], total hip BMD decreased by 0.037 gm/cm². Moreover, hyponatremia was independently associated with increased odds of osteoporosis (Tscores<−2.5) at the hip (odds ratio=2.85; 95% CI 1.03-7.86, p<0.01). Additional studies using an animal model of SIADH have studied multiorgan consequences of chronic hyponatremia in aged rats. Hyponatremic rats developed hypogonadism, as indicated by slightly lower serum testosterone and higher serum FSH and LH concentrations, markedly decreased testicular weight, and abnormal testicular histology. Aged hyponatremic rats also manifested decreased body fat, skeletal muscle sarcopenia by densitometry, and cardiomyopathy manifested as increased heart weight and perivascular and interstitial fibrosis by histology. These findings are consistent with recent results from our laboratory in cultured osteoclastic cells, indicating that low extracellular sodium concentrations increased activity in oxidative stress pathways, thereby potentially exacerbating and accelerating multiple manifestations of age-related senescence. Future prospective studies in patients with SIADH may indicate whether these multiorgan age-related comorbidities may potentially contribute to long-standing observations of increased incidences of morbidity and mortality in this vulnerable population.

Learning Objectives:
- Upon completion of this presentation the participant will be able to: 1) define the clinical consequences of hyponatremia; 2) describe indications for vasopressin receptor antagonists in the therapy of hyponatremia.
- Upon completion of this presentation the participant will be able to: apply these therapeutic issues to the management of hyponatremia in the participant’s practice.

Literature References:
PSYCHOMOTOR SYMPTOMATOLOGY OF HYPONATREMIA

Arthur J. Siegel, MD
McLean Hospital, Belmont, MA

Symptoms of hyponatremia may mimic cognitive and psychomotor disturbances associated with many psychiatric conditions and also may arise as adverse effects of many psychotropic drugs used in treatment. The clinical and laboratory evaluation of hyponatremia, defined by a serum [Na+] concentration < 135 mmol/L, is reviewed including:
- Primary polydipsia hyponatremia syndrome due to fluid intake in excess of the renal capacity for free water excretion.
- Inappropriate antidiuresis [syndrome of inappropriate antidiuretic hormone secretion (SIADH)] dysregulation of arginine vasopressin (AVP) secretion.

Acute and chronic hyponatremic states are associated with excess morbidity and mortality as may be their respective treatments:
- Osmotic demyelination syndrome from rapid correction of chronic hyponatremia may lead to central pontine and extra-pontine myelinolysis.
- Permanent brain injury or death may result from inadequate treatment of acute cerebral edema.

Hyponatremia arising from inappropriate antidiuresis may benefit from treatment with selective AVP2 receptor antagonists as pure ‘aquaretics’.

Learning Objectives:
- To review the neuroendocrine determinants of body fluid homeostasis.
- To understand the underlying pathophysiology of hyponatremic disorders including the role of inflammation leading to inappropriate antidiuresis.
- To review the efficacy and safety of evidence-based treatments to minimize risk for neurological impairment from under and over aggressive interventions.

Literature References:
- Walkers SS, Mount DB, Curhan GC. Mortality after hospitalization with mild.
- Siegel AJ, Baldessarini RJ, Klepser MB, McDonald JC. Primary and drug.
- Siegel AJ. Hyponatremia in Psychiatric Patients: Update on Evaluation and Management.

FLUID BALANCE DISORDERS IN THE ELDERLY

Myron Miller, MD
Johns Hopkins Bayview Medical Center

Normal aging is associated with alterations in the homeostatic systems involved with regulation of water and electrolyte balance. These regulatory components of fluid balance include thirst perception, renal function and hormonal activity, especially the actions of antidiuretic hormone (ADH), atrial natriuretic peptide (ANP) and aldosterone. The confluence of normal aging changes, diseases common in the elderly and the administration of many classes of drugs can lead to the development of hyponatremia with resultant symptomatic consequences. Of all age groups, the incidence of hyponatremia is greatest in the elderly. In community residing elderly, hyponatremia is present in 7-10% over the age of 65 years. These numbers increase to over 20% of elderly hospital patients and as high as 50% of nursing home residents. This presentation will discuss the age-associated alterations predisposing to hyponatremia, epidemiology of hyponatremia, the diseases and drugs associated with the development of hyponatremia and the consequences of hyponatremia in the elderly person.

Learning Objectives:
- Understand the changes of normal aging which predispose the elderly to development of hyponatremia.
- Understand the regulatory systems responsible for the maintenance of body water and electrolyte balance.
- Be able to identify diseases and drugs which can cause hyponatremia in the elderly.
- Understand the consequences of hyponatremia in the elderly.

Literature References:
HYPONATREMIA IN PSYCHOSIS AND DEPRESSION: TREATMENT GUIDELINES AND FUTURE DIRECTIONS

Richard C. Josiassen, PhD
Drexel University College of Medicine, Conshohocken, PA

Background: Chronic hyponatremia (serum sodium concentration [Na+] < 136 mEq/L) is a common life-threatening electrolyte disorder observed in patients with mental illnesses. Early manifestations of the disorder (e.g., headache, nausea, lethargy, restlessness, and confusion) are nonspecific and can be mistaken for aspects of the primary psychiatric disorder itself. As a result, chronic hyponatremia within the psychiatric context often goes unrecognized and unmanaged until the patient becomes severely agitated or has a seizure secondary to a precipitous drop in serum [Na+]. Fluid restriction has been the treatment of choice for chronic hyponatremia to avoid worsening of the clinical condition, but the potential therapeutic benefits of this approach are often undermined by poor patient compliance in psychotic populations. Moreover, the approach is slow to work and difficult to fine-tune. Others have suggested treatment with oral sodium chloride tablets or electrolyte-containing beverages. When fluid restriction or sodium supplementation fails to normalize serum [Na+] most psychiatrists do not initiate further treatment (e.g., sodium supplementation, loop diuretics, demeclocycline) due to the prevailing view that mild to moderate chronic hyponatremia is benign. However, mild chronic hyponatremia may not be benign. A small, but growing body of recent research suggests that mild hyponatremia is associated with gait and attentional impairment contributing to an increased rate of falls, decreased bone mineral density and increasing bone fragility, and increased risk for subsequent development of acute hyponatremia. Thus, if not effectively treated, chronic hyponatremia may have a negative impact on therapeutic outcomes and long-term quality of life in this population.

Methods: Psychiatric patients with chronic hyponatremia enrolled in three multicenter, double-blind studies of vaptan antagonists. All subjects had evidence of impaired water excretion. Minor design differences existed, but study assessments occurred on Day 1 (baseline and 8 hours after the first dose), Day 2 through 4 (or end of titration), and Day 30; and a 7 Day follow-up visit. Safety was assessed at all visits.

Results: Mean serum [Na+] in vaptan-treated patients normalized within 24 hours. No drug-related adverse events led to study discontinuation.

Conclusion: Chronic hyponatremia has deleterious effects on quality of life for individuals with mental illness. These results suggest that oral vaptans provide rapid, effective, and safe treatment of chronic hyponatremia and that the effect is safely sustained over time.

Learning Objectives:
- Participants will recognize early manifestations of mild-moderate hyponatremia
- Participants will learn about cell volume regulation and the role of glutamate
- Participants will appreciate the developing approaches for treating hyponatremia

Literature References:
PANEL OVERVIEW:
NEW OPPORTUNITIES AND STRATEGIES FOR NIMH FUNDING

Christopher Sarampote, PhD, Aileen Schulte, PhD, Michael Kozak, PhD, Tracy Waldock, PhD, Jean Noronha, PhD
National Institute of Mental Health

With the changing landscape of NIH research funding, prospective investigators need to be aware of NIMH priorities, familiarize themselves with the procedures for successful grant submission and review, and stay informed of the latest developments and notices regarding the submission process. This session is designed to provide information to help investigators navigate the many changes that have taken place in the past few years in how NIH receives, reviews, and funds grant applications.

This panel of NIMH staff will discuss helpful techniques to transform research questions into competitive applications and to clearly communicate ideas to reviewers and the Institute. In addition, special focus will be placed on highlighting NIMH priorities, including the Dimensional Approaches to Research Classification in Psychiatric Disorders (RDoC) and initiatives growing from the Council Workgroup report From Discovery to Cure: Accelerating the Development of New and Personalized Interventions for Mental Illnesses. In addition, an overview of the NIH process from submission to award will be presented.

The workshop will also provide a Q&A session with NIMH review, program, and policy staff members to provide more specific information and discussion on the development, submission, and review of applications with the goal of an NIMH funded grant.

Learning Objectives:
- Understand the NIH Application and Review Process
- Learn to navigate the NIMH website and other resources to find funding information and information to aid in the preparation of a competitive NIMH application
- Learn strategies to turn a great idea into a successful application and how to respond to a summary statement
- Learn about NIMH funding priorities

DEMYSTIFYING REVIEW AT NIMH

Aileen Schulte, PhD
National Institute of Mental Health, Rockville, MD

With the changing landscape of NIH research funding, prospective investigators need to be aware of NIMH priorities, familiarize themselves with the procedures for successful grant submission and review, and stay informed of the latest developments and notices regarding the submission process. This session is designed to provide information to help investigators navigate the many changes that have taken place in the past few years in how NIH receives, reviews, and funds grant applications.

The workshop will also provide a Q&A session with NIMH review, program, and policy staff members to provide more specific information and discussion on the development, submission, and review of applications with the goal of an NIMH funded grant.

Learning Objectives:
- Understand the NIH Application and Review Process
- Learn to navigate the NIMH website and other resources to find funding information and information to aid in the preparation of a competitive NIMH application

Literature References:
DIMENSIONAL APPROACHES TO RESEARCH CLASSIFICATION IN PSYCHIATRIC DISORDERS (RDoC)

Michael Kozak PhD
National Institute of Mental Health, Rockville, MD

Conventional psychiatric diagnosis, based on clinical presentation and course, might have limited the contributions of recent findings from integrative neuroscience research to psychopathology, in that conventionally established clusters of complex behaviors have been difficult to relate to biological systems. The National Institute of Mental Health's Research Domain Criteria (RDoC) project proposes a new heuristic for organizing research, to facilitate the integration of advances in biology with psychopathology. This approach advocates new methods for ascertaining samples, such that research targets are not conventional diagnostic categories, but rather, dimensional domains hypothesized to be mechanisms of psychopathology. The focus of the RDoC initiative is putative psychological and biological mechanisms that drive psychiatric symptoms. It is designed to uncase research from some constraints that might have impeded progress.

Learning Objectives:
- Rationale for RDoC initiative
- Fundamentals of RDoC approach
- Current status of RDoC initiative

Literature References:
- Sanislow CA, Pine DS, Quinn KJ, Kozak MJ, Garvey MA, Heinssen RK.

INNOVATIVE PILOT STUDIES OF NOVEL MECHANISM OF ACTION COMPOUNDS FOR TREATING PSYCHIATRIC DISORDERS

Christopher Sarampote PhD
National Institute of Mental Health, Rockville, MD

The translation of promising novel therapeutic targets into effective treatments for mental disorders has been disappointingly slow. NIH efforts to promote such development have included work by the National Advisory Mental Health Council to provide guidelines and recommendations for researchers, summarized in the report, From Discovery to Cure: Accelerating the Development of New and Personalized Interventions for Mental Illness. A recommendation identified in this report was for NIH to invest in early stage clinical trials of novel compounds which act on novel molecular pathways that are not targeted with currently available psychiatric drugs. This talk will summarize a recent NIH program announcement aimed to accelerate the clinical development of new mechanism of action candidate medications to treat mental disorders through first in human (FIH) and proof of concept (POC) studies using experimental medicine approaches. Examples of work supported by this announcement will be provided.

Learning Objectives:
- Attendees will be able to identify NIH resources for novel psychiatric drug development.
- Attendees will be able to identify steps for producing more efficient, mechanism-based therapeutic development programs.

Literature References:
LATE BREAKING NEWS FROM NIMH
Tracy Waldeck, PhD
National Institute of Mental Health, Rockville, MD

With the changing landscape of NIH research funding, prospective investigators need to be aware of NIMH priorities, familiarize themselves with the procedures for successful grant submission and review, and stay informed of the latest developments and notices regarding the submission process. This session is designed to provide information to help investigators navigate the many changes that have taken place in the past few years in how NIH receives, reviews, and funds grant applications. This panel will also discuss effective techniques for transforming research questions into competitive applications and for presenting ideas to reviewers and the Institute. Special focus will be placed on reviewing NIMH priorities and highlighting two recent priorities: Dimensional Approaches to Research Classification in Psychiatric Disorders (RDoC) and initiatives growing from the Council Workgroup report From Discovery to Cure: Accelerating the Development of New and Personalized Interventions for Mental Illnesses. In addition, an overview of the NIH process from submission to award will be presented.

The workshop will also provide a through a Q&A session, NIMH review, program, and policy staff members will provide more specific information and discussion on the development, submission, and review of applications with the goal of an NIMH funded grant.

Learning Objectives:
- Understand the NIH Application and Review Process
- Learn strategies to turn a great idea into a successful application and how to respond to a summary statement
- Learn about NIMH funding priorities

Literature References:
- [NIMH Web page](http://www.nimh.nih.gov/research-funding/grants/writing-approval-process/index.shtml)
- [CSR Web page](http://grants.nih.gov/grants/peer-review-committees.shtml)
- [NIMH Strategic Planning Reports](http://www.nimh.nih.gov/research-funding/research-priorities/nimh-strategic-research-priorities.shtml)

CATCHING AND SHEPHERDING YOUR APPLICATION
Jean G. Noronha, PhD
National Institute of Mental Health, Bethesda, MD

Learn the key steps to ensuring a successful grant application submission as well as obtaining the preferred institute and study section assignments for your application. Learn also what to do/who to contact if you do encounter a problem in submission or assignment.

Learning Objectives:
- Key steps to a successful grant submission
- How NIH determines assignment to institutes and review groups
- How to address problems that arise in this process

Literature References:
- [NIMH Web page](http://www.nimh.nih.gov/research-funding/grants/writing-approval-process/index.shtml)
- [CSR Web page](http://grants.nih.gov/grants/peer-review-committees.shtml)
Tuesday, May 29, 2012

PANEL
9:00 A.M. - 10:30 A.M.

PANEL OVERVIEW:
COMMON TARGETS FOR THE TREATMENT OF SUBSTANCE USE DISORDERS AND CO-OCCLUDING PSYCHIATRIC DISORDERS

David McCann\textsuperscript{1}, PhD, Wilson Compton\textsuperscript{1}, MD, Lawrence Tolf\textsuperscript{1}, PhD, Linda Rorick-Kehn\textsuperscript{1}, PhD, Phil Skolnick\textsuperscript{1}, PhD

\textsuperscript{1}NIH/NIDA, \textsuperscript{2}Torrey Pines Institute for Molecular Studies, \textsuperscript{3}Lilly

Among patients with substance use disorders (SUDs), poly-substance use is more common than the use of a single substance. Moreover, about half of patients with SUDs are afflicted with other types of psychiatric disorders. Treatment of these co-occurring disorders poses a significant challenge for healthcare providers. For example, depression and anxiety disorders (which may be antecedent to initial drug use or a consequence of drug-induced changes in the brain) can serve to promote drug use and prevent patients from achieving or maintaining abstinence. Medications capable of treating multiple types of substance use disorders, as well as co-occurring psychiatric disorders, are clearly desirable. The first presentation of this panel session will describe the prevalence of co-occurrence among substance use disorders and other psychiatric disorders, as well as current treatment approaches. Subsequent presenters will focus on three targets that hold promise for advancing treatment options in this difficult area of psychiatry: Nociceptin/Opioid FQ Peptide (NOP) receptor agonists, kappa-opioid receptor antagonists, and norepinephrine uptake inhibitors.

Learning Objectives:
- Gain a better understanding of the prevalence of poly-substance use and co-occurring psychiatric disorders, as well as current treatment approaches.
- Become familiar with targets/medications that hold the promise of advancing treatment options for patients afflicted with polydrug dependence and co-occurring psychiatric disorders.

SUBSTANCE USE DISORDERS AND CO-OCCLUDING PSYCHIATRIC DISORDERS: PREVALENCE AND CURRENT TREATMENT APPROACHES

Wilson Compton, MD, Ivan D. Montoya, MD
National Institute on Drug Abuse, Bethesda, MD

Comorbidity denotes the simultaneous presence of more than one distinct clinical entity in an individual. The comorbidity of substance use disorders (SUD) with other psychiatric disorders is more the rule than the exception. It has been reported that more than half of individuals with SUD also have at least one serious mental illness. Conversely, among people diagnosed with mental disorders, some SUDs can be present as often as in 90% of them. When SUDs and psychiatric disorders co-occur, patients are more likely to have difficulty initiating/maintaining drug use abstinence and controlling the psychiatric symptoms, to have medical and psychosocial complications, to utilize health services, and to attempt or commit suicide. A thorough evaluation of SUD and psychiatric complaints is critical to determine the multiple needs of this population and develop a multidisciplinary treatment approach, which usually includes pharmacological and non-pharmacological interventions. It has been reported that some comorbid conditions may share a neurobiological substrate and, therefore, medications may be effective to treat these comorbid conditions. The purpose of this presentation is to review the prevalence of co-occurring SUD and psychiatric disorders, their current treatment approaches, and the opportunities to study pharmacotherapies to simultaneously treat comorbid disorders.

Learning Objectives:
- To review the prevalence of co-occurring SUD and other psychiatric disorders.
- To gain knowledge about current treatment approaches for comorbid disorders.
- To discuss potential pharmacotherapies to simultaneously treat comorbidities.

Literature References:
BUPROPION: BEYOND SMOKING CESSATION AND DEPRESSION

David J. McCann, PhD
NIH/NIDA, Bethesda, MD

Bupropion, already approved for the treatment of depression and tobacco dependence, has shown promising results in the treatment of methamphetamine dependence and attention deficit disorders. In a human laboratory study, bupropion (150 mg twice daily) was reported to blunt both the subjective and cardiovascular effects of intravenous methamphetamine and to decrease drug craving. In two 12-week, placebo-controlled trials (one single-site and one multisite), bupropion treatment (150 mg twice daily) was reported to reduce methamphetamine use among study participants reporting < 18 days of methamphetamine use during the 30 days immediately prior to screening. A responder-based reanalysis of the published multi-site trial, with achievement of two or more weeks of end-of-study abstinence required for “success,” revealed a significant effect of bupropion in the total study population. This presentation will summarize the above findings and report the results of a second multi-site trial of bupropion vs. methamphetamine dependence. The possibility of a common molecular target for bupropion’s multiple therapeutic applications will also be discussed.

Learning Objectives:
- Become familiar with two potential indications for the use of bupropion other than smoking cessation and the treatment of depression.
- Gain a better understanding of the molecular targets that are likely to be engaged by bupropion at clinically relevant doses.

Literature References:

NCP RECEPTORS AS TARGETS FOR THE TREATMENT OF DRUG ADDICTION AND CO-OCcurring PSYCHIATRIC DISORDERS

Lawrence Toll, PhD
Torrey Pines Institute for Molecular Studies, Port St. Lucie, Florida

The NOP receptor is the fourth member of the opioid receptor family. The NOP receptor and its endogenous ligand nociceptin (N/OFQ) are highly expressed in brain regions implicated in pain, drug abuse and anxiety. Although N/OFQ is in the opioid peptide family, it blocks opiate analgesia when administered i.c.v. Unlike opiates, it does not increase extracellular dopamine levels in the nucleus accumbens, but blocks a dopamine increase induced by a variety of abused drugs. N/OFQ also blocks self-administration and/or conditioned place preference (CPP) of a large number of abused drugs including morphine, cocaine, methamphetamine, and alcohol. N/OFQ, when administered i.c.v. also attenuates anxiety in a variety of preclinical animal models. Upon the synthesis of NOP receptor agonists and antagonists, they were tested in animal models as potential treatments for drug abuse, anxiety, and depression. Both small molecule (administered systemically) and peptide (administered i.c.v.) agonists have been shown to have anxiolytic activity and to block CPP induced by morphine and self-administration of alcohol. In addition, NOP receptor antagonists appear efficacious as antidepressants in animal models of depression. These results demonstrate that NOP receptor-active compounds could have clinical efficacy as medications for drug abuse and psychiatric disorders.

Learning Objectives:
- Become familiar with the fourth receptor in the opioid receptor family, NOP and its endogenous ligand N/OFQ.
- Understand the usefulness of the NOP receptor as a target for drug abuse and psychiatric disorders.

Literature References:
PANEL
9:00 A.M. - 10:30 A.M.

PRECLINICAL PHARMACOLOGICAL CHARACTERIZATION OF
STRUCTURALLY UNIQUE, POTENT, KAPPA OPIOID RECEPTOR
ANTAGONISTS IN ANIMAL MODELS OF ALCOHOL DEPENDENCE AND
MOOD DISORDERS

Linda M. Rorick-Kehn, PhD
Lilly Research Laboratories, Indianapolis, IN

Kappa opioid receptors and their endogenous neuropeptide ligand, dynorphin A, are densely localized in limbic and cortical areas comprising the brain reward system, and play a key role in modulating stress and mood (1). Prolonged activation of kappa receptors by dynorphin (resulting from chronic stress or repeated drug use) leads to a pro-depressive phenotype and promotes further drug use (2). Growing literature indicates that kappa receptor antagonists may be beneficial in the treatment of mood and addictive disorders. FP3FBZ and LY2456302 are structurally-unique, potent, kappa opioid receptor antagonists with selectivity over mu/delta and other non-opioid receptors. Both compounds exhibit canonical pharmacokinetic properties that are favorable for clinical development. In behavioral models, both FP3FBZ and LY2456302 potently reduce high ethanol self-administration behavior in alcohol-prefering (P) rats and, unlike naltrexone, do not exhibit significant tolerance with repeated dosing. Additionally, and in contrast to naltrexone, FP3FBZ and LY2456302 also produced antidepressant- and anxiolytic-like effects in rodent models. Collectively, the preclinical data indicate that FP3FBZ and LY2456302 are centrally-penetrant, potent, kappa-selective antagonists with efficacy in animal models of predictive of antiaddictive, antidepressant- and anxiolytic-like efficacy. In contrast to currently available therapies, the present data suggest that antagonism of kappa opioid receptors may provide therapeutic benefit in the treatment of both alcohol dependence and depressive disorders.

Learning Objectives:
- Explore in vitro and in vivo data on two novel kappa-selective antagonists with pharmacokinetic properties that differ from kappa antagonists in the literature.
- Discuss broad therapeutic potential of kappa-selective opioid antagonists relative to currently available therapeutics.

Literature References:
Tuesday, May 29, 2012

PANEL
9:00 A.M. - 10:30 A.M.

PANEL OVERVIEW: RESEARCH DOMAIN CRITERIA (RDoC): IMPLICATIONS FOR RANDOMIZED CLINICAL TRIALS

Robert Heinssen¹, PhD, Sarah Morris¹, PhD, Richard Keeffe², PhD, Robert Levin³, MD

¹NIH, ²Duke, ³FDA

Over recent decades, an increasingly comprehensive body of research in genetics, neuroscience, and behavioral science has transformed our understanding of how the brain produces adaptive behavior, and the ways in which healthy functioning becomes disrupted in people with classically defined mental disorders. The NIMH Strategic plan includes a specific objective that encourages research to speed the translation of this new knowledge to clinical issues: “Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures.” The implementation of this strategy is named the Research Domain Criteria Project (RDoC). NIMH envisions RDoC as the beginning of a long-term effort to apply advances in genomics, cognitive and affective neuroscience, and systems biology to deepen our understanding of mental illness pathophysiology, and for developing new approaches to diagnosis and treatment. The current panel will consider the goals, scientific activities, and accomplishments of RDoC to date, as well as their implications for the next generation of clinical trials. Critical issues related to subject recruitment and selection, baseline assessment, delivery of interventions, and outcome evaluation will be discussed. Regulatory issues, such as FDA requirements for indications within the RDoC framework, will be considered.

Learning Objectives:
- Following this presentation, audience members will be able to list 2 ways in which a neuroscience-based system for classifying mental disorders could improve clinical diagnosis and treatment.
- Following this presentation, audience members will be able to list 1 RCT methods and 1 FDA regulatory challenge that must be surmounted by the Research Domain Criteria (RDoC) initiative.

INTRODUCING THE NIMH RESEARCH DOMAIN CRITERIA PROJECT (RDOC)

Sarah Morris, PhD
National Institute of Mental Health, Bethesda, MD

The NIMH Research Domain Criteria (RDoC) initiative provides a framework for researchers to reorient their approach to the study of mental disorders by incorporating a focus on dimensional characterizations of symptoms and illness and structuring the examination of relationships between different levels of analysis, with an anchoring emphasis on neural circuits. The centerpiece of the initiative is a matrix of dimensions of observable behavior and neurobiological measures with corresponding constructs and cross-cutting units of analysis. The intersections of constructs and units of analysis are populated by elements that are derived from prior and ongoing research efforts, thus providing a structure for the organization of existing knowledge and a guide for future efforts to fill in research gaps. This presentation will include an overview of the background and impetus for the RDoC initiative, an introduction to the RDoC conceptualization and matrix and an update on the activities of the NIMH RDoC working group.

Learning Objectives:
- Upon the completion of this lecture the participants will understand the goals of the NIMH RDoC initiative and how this approach differs from categorical diagnostic approaches.
- Upon the completion of this lecture the participants will be able to identify the domains and the units of analysis of the RDoC matrix.

Literature References:
CONCEPTUALIZING CLINICAL TRIALS WITHIN THE RDOC FRAMEWORK

Richard Keefe, PhD
Duke, Durham, NC

Traditional clinical trials methodology has dictated that subjects meet criteria for specific diagnostic entities as defined by accepted nomenclature, usually the Diagnostic and Statistical Manual (DSM). This approach emphasizes the organization of patients based upon historical precedents and conceptual frameworks that may have little relation to the underlying neurobiology of mental disorder. Application of the Research Domain Criteria (RDoC) in clinical trials will require that patients are organized based upon dimensions of observable behavior and neurobiological measures. This new approach will have a dramatic impact on various aspects of clinical trials methodology such as the application of inclusion criteria, patient recruitment, effect size estimates and statistical power. This presentation will discuss the implications of conducting clinical trials using the RDoC approach. Identification of individuals for treatment studies based upon the underlying neurobiology of behavioral disturbance rather than conceptual and historical diagnosis will require significant advances in the identification of the specific neural circuits that underlie specific aspects of human behavioral disturbance and suffering. However, these advances will enable the development of targeted treatments that can be applied directly to specific CNS disturbance. Since patients without the specific neurobiological disturbance will not be included in clinical trials applying this type of targeted approach, these trials are likely to have an enhanced statistical power to demonstrate significant neurobiological benefit. They also may be challenged to demonstrate that these specific interventions have an impact on global functioning. The development of outcome measures for these trials will need to weigh neurobiological specificity and global patient benefit.

Learning Objectives:
- To receive an update on the current status of work on the Research Domain Criteria (RDoC)
- To understand the strengths and limitations of applying the RDoC in clinical trials settings

Literature References:

FDA PERSPECTIVE: REGULATORY CONSIDERATIONS FOR RDOC-INSPIRED TRIALS

Robert Levin, MD
FDA, Silver Spring, MD

The Research Domain Criteria initiative can stimulate novel approaches to understanding disease states and their connection with the phenomenology of psychiatric conditions. Ultimately, this may lead to greater diagnostic precision, targeted treatments, and improvements in outcomes. Clearly there are limitations with the current systems of diagnosis and classification. For at least some of the currently recognized psychiatric disorders, it seems that these may be syndromes as opposed to distinct biological disorders. Features of various psychiatric disorders have significant overlap in phenomenology. As our understanding grows regarding the biological mechanisms underlying brain function, there are increasing opportunities for novel research as well as the development of more specific and effective treatments.

In providing the FDA’s perspective on the RDoC initiative, we will discuss: the process for drug development, potential study designs for RDoC-inspired trials, developing and validating biomarkers, and incorporating biomarkers in clinical trials. This will also include a discussion of potential indications related to RDoC.

Learning Objectives:
- Upon completion of this discussion, participants will understand the regulatory requirements for obtaining indications
- Upon completion of this discussion, participants will understand the FDA perspective on developing biomarkers and incorporating them in clinical trials
- Upon completion of this discussion, participants will understand FDA’s potential ongoing role in the RDoC initiative

Literature References:
A RESEARCH TOOL TO ASSESS AGE-RELATED DECLINES IN COGNITIVE FUNCTION

Keith A. Wesnes1,2, BS, PhD; Brian Saxby1, BS, PhD
1Bracket, Goring on Thames, United Kingdom; 2Swinburne University, Melbourne, Australia, University of Newcastle, Newcastle, United Kingdom

Introduction: The deficits to cognitive function which occur in normal aging can potentially be treated with pharmaceutical products. Further, as criteria have now been proposed for pre-clinical dementia (Sperling et al., 2011), trials are now being planned with compounds designed to prevent or reduce cognitive decline in groups of healthy volunteers identified to be at risk of developing Alzheimer's disease. However, in order to conduct such trials, cognitive tests need to be employed which can reliably assess such change. In the present study a cohort of healthy elderly volunteers was assessed yearly over a 5 year period with a computerised test battery.

Methods: The CDR System is a computerised set of 9 tests of attention, working and episodic memory which has been widely used in trials of potential cognitive enhancers in healthy volunteers, age-related cognitive decline, MCI and the dementias. 256 normative volunteers (113 females), mean age 76 years (range 70 to 90), mean MMSE 28.8 (range 23 to 30), were trained on the CDR System twice before a baseline was established, and then restaged yearly for up to 5 years.

Results: Validated composite factor scores were derived from the various test measures. Performance was found to decline significantly over the study period on four of the five scores: power of attention (p<0.0001), quality of episodic recognition memory (p<0.0002), quality of working memory (p<0.015) and speed of retrieval of information held in memory (p<0.0001). Power of attention showed significant deficits from year one onwards, two other measures showed deficits by year one, and all showed significant deficits from year three onwards.

Conclusions: This study has demonstrated that the use of validated and sensitive tests of cognitive function can detect decline over a 5-year period in healthy elderly volunteers. Such testing is therefore fit for purpose for the evaluation of treatments aimed at preventing or even reversing age-related declines in cognitive function, as well as treatments which may delay the onset of Alzheimer's disease in high risk but otherwise healthy populations.

Learning Objectives:
- Appreciate how cognitive function can be assessed longitudinally
- Examine the patterns of decline in the elderly over 5 years
- Evaluate the suitability of computerised testing in preclinical dementia research

Literature References:

ADVERSE EVENTS IN REGULATORY CLINICAL TRIALS OF SECOND GENERATION ANTIHYPERTENSIVES: CHANGES OVER TIME DURING THE PAST TWO DECADES

Laszlo Tombor1, MD, Szilvia Papp2, MD, Brigitta Kakuszi2, BS, Pal Czobor2, PhD
1Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Budapest, Hungary; 2Nathan Kline Institute for Psychiatry Research, Orangeburg, NY

Background: Second generation antipsychotics are used worldwide in the treatment of schizophrenia and other mental disorders with psychotic symptoms, and offer an effective and relatively well tolerated treatment option. Despite their good therapeutic effect, treatment-emergent adverse events and side effects during everyday clinical use are common, often leading to treatment discontinuation (1) or frequent changes of medication (2).

Objectives: Our goal was to delineate changes over time in regulatory clinical trials of atypical antipsychotics during the past two decades in the incidence rates of study drug discontinuation due to adverse events (adverse dropouts), and the most common adverse events during the new drug approval.

Methods: Open-access, Summary Basis of Approval documentation of all successful New Drug Applications, available at the website of the U.S. Food and Drug Administration (FDA) constituted the principal source of information for this investigation. Safety data including treatment-emergent adverse events, adverse dropouts, common side effects and other safety events for this investigation were available for nine second generation antipsychotics (risperidone, aripiprazole, asenapine, olanzapine, paliperidone, quetiapine, iloperidone, lurasidone, ziprasidone), approved between 1993 and 2010 for safety data. Statistical analyses were based on random regression, hierarchical linear model modeling and correlation analyses.

Results: We found a significant positive correlation of the incidence of adverse dropouts with time both for test medication (r=0.32, p=0.018) and for placebo (r=0.39, p=0.028). In addition, our results indicated a significant positive correlation between the incidence of adverse events and consent withdrawal for test medication (r=0.35, p=0.009), which was stable over time.

Conclusions: Incidence of adverse dropouts showed a steady increase over time during the past two decades in regulatory clinical trials of second generation antipsychotics both in the test and the placebo arms. This finding has implications both for the design of clinical trials for new drug development, and for the regulatory evaluations of safety information from future clinical studies.

Learning Objectives:
- Antipsychotics
- Side effects

Literature References:
ARE LARGE NUMBERS OF INVESTIGATIVE SITES ASSOCIATED WITH SYMPTOM IMPROVEMENT ON PLACEBO IN ANTIPSYCHOTIC RANDOMIZED CONTROLLED TRIALS (RCTS)? A META-ANALYTIC REVIEW

Robert Litman¹, MD, Susan Szymialis², BS, Arif Khan³, MD
¹CBH Health, LLC, Rockville, MD, ²Northwest Clinical Research Center, Bellevue, WA

Introduction: Improvement on placebo treatment observed in recent atypical antipsychotic RCTs in schizophrenia has been attributed to excessive variability in study design factors, including number and nature of investigative sites. We hypothesized that studies utilizing large numbers of sites would lead to greater improvement on placebo treatment.

Methods: We abstracted data on site number and response to placebo from recently published antipsychotic trials by searching MEDLINE, Clinicaltrials.gov, and the Cochrane Database for placebo-controlled RCTs of atypical antipsychotics in schizophrenia. Search terms were schizophrenia, placebo, and generic names for all antipsychotics agents submitted for FDA approval from 1993-2010. Only trials utilizing the PANSS were analyzed. Response to placebo treatment, expressed as a percentage of the baseline score, was defined as the change in PANSS on placebo/PANSS baseline score for the placebo arm, and was correlated (Pearson's R, 1-tailed) with the number of investigative sites for each RCT.

Results: We found 31 RCTs for aripiprazole, asenapine, bifeprunox, iloperidone, lurasidone, olanzapine, paliperidone,quetiapine, risperidone, sertindole and ziprasidone. One trial for asenapine and one trial for iloperidone were omitted from analysis for lack of PANSS baseline data. Number of sites and the change in PANSS/PANSS baseline score were negatively correlated ($r = -0.33$, $p = 0.04$), indicating that higher site numbers were associated with greater improvement on placebo. Number of sites utilized per RCT increased over time ($r = 0.53$, $p<0.01$, 2-tailed).

Conclusion: These data support a possible association between the recent increase in placebo response and the increase in numbers of sites in antipsychotic RCTs. Further research regarding variability due to site and other study design elements is warranted.

Learning Objectives:
- Understand importance of placebo response for drug development.
- Understand RCT design factors which contribute to placebo response.

Literature References:
- Kemp, A.S., et al. What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it? Schizophrenia Bull 2008; 36:504-509.

PREDICTION OF SUICIDE IN CLINICAL TRIALS USING THE C-SSRS

Kelly Posner PhD
Columbia University, NYS Psychiatric Institute, New York, NY

Prospective assessment of suicidal issues has become a focus across drug development, and innovative methods to assess these outcomes have been developed. The importance of prediction cannot be underestimated [1]. Suicidal ideation and behavior are prevalent across all medical disorders (25.2% have ideation; 8.9% make an attempt) further rendering feasible, prospective assessment a priority for all drug development programs. This presentation will review evidence on prospective risk for suicidal behavior during trial participation, including data demonstrating predictive validity of the C-SSRS in adolescents, where the Beck SSI did not [2]; patients with higher severity of ideation on C-SSRS were 50% more likely to attempt suicide. The data also predictively supported clearly delineated thresholds for triggering next steps, ultimately redirecting limited resources where they need to go, streamlining study conduct by enabling better identification of subjects who need referrals, and avoiding unnecessary exclusions. These predictive findings have been supported in adults, with data from over 35,000 electronic administrations (eC-SSRS) across development programs. These showed that participants reporting prior severe suicidal ideation or prior suicidal behavior were 4.5 times more likely to report suicidal behavior during study. Participants who reported both were 8 times more likely. This presentation will include data from an analysis of 50,000 administrations and will present data on the predictability of increases in severity levels of ideation, i.e., the predictability of increases from one score to a higher score.

Investigators do not routinely ask about important suicidal behaviors, yet the results of the electronic administrations showed 70 reported attempts, but also 178 interrupted attempts, 233 aborted attempts, and 71 acts of reported preparatory behavior. These behaviors were typically not asked about before. The presentation will review the evidence for prediction, why the instrument shows predictive validity, and discuss ramifications for streamlining study conduct.

Learning Objectives:
- Understand improved precision in prediction in assessment
- Understand how these improved methods can facilitate study conduct, leading to reduced burden, referrals, and exclusions.

Literature References:
PERSONALIZED THERAPY WITH ADJUNCTIVE L-METHYLFOlate IN PATIENTS WITH SSRI-RESISTANT DEPRESSION

Maurizio Fava, MD, George I. Papakostas, MD, John M. Zajecka, MD, Richard C. Shelton, MD

1Massachusetts General Hospital, Boston, MA; 2Rush University Medical Center, Chicago, IL; 3Vanderbilt University, Nashville, TN

Objective: Evaluate the use of biomarkers to determine the response to adjunctive L-methylfolate 15 mg among patients with an inadequate response to SSRIs.

Methods: 75 outpatients with SSRI-resistant MDD were enrolled in a 60-day, multi-center, double-blind, placebo-controlled trial divided into two 30-day phases. Patients were randomized to receive L-methylfolate 15 mg/day for 60 days, placebo for 30 days followed by L-methylfolate 15 mg/day for 30 days or placebo for 60 days. Secondary genomic and biomarker endpoints were evaluated for their association with treatment effect.

Results: Increased efficacy was observed with adjunctive L-methylfolate 15 mg/day vs. SSRI therapy plus placebo (pooled difference in response rates on the HAM-D 17 (17.7%, p=0.04)). Pooled differences in mean change on HDRS-17 and HDRS-28 were significantly different (p=0.05 and p=0.02, respectively). Treatment effects were similar in patients with baseline L-methylfolate levels below vs. above the median. A numerically greater treatment effect was observed in patients with an allelic variant in the MTHFR (methylene tetrahydrofolate reductase) C677T genotype (difference in mean change in HDRS-28 of -3.75 for T allele (homozygotes and heterozygotes combined) vs. 1.99 for C allele). Patients with a BMI >30 kg/m² experienced a significantly greater reduction in depressive symptoms with L-methylfolate (difference in mean change in HDRS-28 of -4.66; p=0.001).

Conclusion: Adjunctive L-methylfolate 15 mg/day may represent an effective and well tolerated adjunct treatment strategy for MDD patients who are SSRI partial- and non-responders, particularly in patients with a BMI >30 kg/m² or with the MTHFR C677T T allele.

Learning Objectives:
- Recognize applications of L-methylfolate therapy for managing patients with MDD who have an inadequate response to antidepressants.
- Recognize the potential for application of individualized therapy with L-methylfolate in depressed patients using biomarkers.

Literature References:
- Ginsberg LD, Oubre A, Daoud Y. L-methylfolate plus SSRI or SNRI from treatment initiation compared to SSRI or SNRI monotherapy in a major depressive episode. Innov Clin Neurosci 2011;8:19-28.
DECYCLOSERINE AUGMENTATION OF CBT FOR SOCIAL ANXIETY DISORDER: RESULTS FROM AN RCT

Mark H. Pollack1, MD, Jasper Smits1, PhD, Naomi M. Simon1, MD, Alicia Meurer2, PhD, Luana Marques1, PhD, David Rosenfeld1, PhD, Michael W. Otto1, PhD, Stefan Hofmann1, PhD

1Rush University Medical Center, Chicago, IL, 2Southern Methodist University, Dallas, TX, 3Massachusetts General Hospital, Boston, MA, 4Boston University, Boston, MA

Background: Accruing translational evidence suggests the efficacy of D-Cycloserine (DCS) to augment CBT for anxiety disorders. We present acute and long-term results from a 3-site RCT of DCS for augmentation of CBT in Social Anxiety Disorder (SAD).

Methods: 170 subjects (LSAS > 60) were randomized to CBT plus DCS (50 mg) or CBT plus placebo, CBT comprised twelve 2.5 hours group sessions, with DCS/placebo administered 1 hour prior to sessions 3-7.

Results: Logistic regression analyses indicate a significant main effect for response at endpoint for DCS, (77.9% vs 64.6%; OR = .44, p < .05). There was also a significant treatment by initial severity interaction, OR=2.99, p=.005. DCS outperformed PBO at moderate severity ( CGI 4/5: 58% of sample, p=.005 at both levels), but was equivalent/slightly worse at more severe levels. Higher severity was associated with poorer outcomes (OR=4.6, p=.01) for DCS but not PBO. For endpoint remission there was a significant main effect for DCS, 34.9% vs. 22.0%; OR=.50, p=.05, with no initial severity interaction. At 6-month FU, there was no main effect for DCS (68.6%, PBO=65.9%, OR=.83, p=.58) on response, though the interaction of treatment and initial severity was significant, OR=2.54, p=.01. DCS tended to outperform PBO at lower initial severity levels with the reverse holding at higher levels. There were no significant remission effects for treatment (DCS=26.7% v PBO: 24.4%), initial severity, nor for their interaction.

Conclusions: Results demonstrate an augmentative effect for DCS in the acute treatment of SAD with evidence of a treatment by initial severity interaction.

Learning Objectives:
- To discuss the rationale for the use of DCS for augmentation of CBT
- To examine the efficacy of DCS augmentation of CBT for Social Anxiety Disorder

Literature References:

A HIGH-THROUGHPUT CLINICAL ASSAY FOR TESTING DRUG FACILITATION OF LEARNING-BASED PSYCHOTHERAPY

Eric J. Lenze, MD, Cheri A. Levinson, MS, Tom L. Rodebaugh, PhD
Washington University, St. Louis, MO

Background: An exciting new direction in the treatment of mental disorders is the preliminary finding that learning-based psychotherapy can be facilitated by medication that enhances learning. Several pilot studies have demonstrated that the NMDA receptor agonist d-cycloserine increases response to exposure therapy in anxiety disorders. We developed a standardized clinical assay to test exposure therapy facilitation, with the goal of testing therapy-facilitating effects of medications in a clinical population more quickly and inexpensively than a traditional clinical trial.

Approach: We developed a standardized brief exposure in which participants with social anxiety disorder gave a brief (~7 minute) videotaped speech in front of an examiner. Participants were randomized to receive a single capsule of 200mg d-cycloserine (N=16) or a matching placebo (N=14) prior to preparation for the speech. Their distress levels were rated during the speech and again, one week later in which they gave a speech in an identical situation. Our primary measure of d-cycloserine’s effect was between-session habituation: whether the participants showed less distress during the second speech compared to the first. We also measured subjective anxiety and fear of scrutiny using validated measures.

Results: As expected, subjects randomized to receive d-cycloserine prior to their first speech were more likely to show between-session habituation than those who received placebo (75% vs. 36%, chi-sq p=.003). We also found greater reduction in prespeach anxiety level and statistical trends for greater amount of reduction of anxiety and fear of scrutiny, in the d-cycloserine group.

Conclusion: Our clinical assay demonstrated exposure-facilitation effects of d-cycloserine in a clinical anxiety population. Most importantly, this assay was able to do so quickly and in a highly standardized way, and could test other medications for similar therapy-enhancing effects using a fraction of the time and costs of a traditional clinical trial. Given the increasing interest in using medications to enhance learning-based psychotherapy, this high-throughput clinical assay approach may be a favorable method for drug testing.

Learning Objectives:
- Present the concept of a “high throughput clinical assay” for drug testing.
- Present data demonstrating that d-cycloserine like effects on exposure therapy facilitation can be tested in a brief clinical assay.

Literature References:
DECREASED OCCIPITAL GLUTATHIONE LEVELS IN TOURETTE'S DISORDER

Vilma Gabbay¹, MD, MS, Barbara Coffey¹, MD, MS, Benjamin A. Ely¹, BS, Amy Alpert¹, Chuqing Kang¹, Dikoma C. Shungu¹, PhD

¹New York University Child Study Center, New York, NY; ²Nathan S. Kline Institute, Orangeburg, NY; ³Weill Cornell Medical College, New York, NY

Background: Tourette's Disorder (TD) is an neuropsychiatric disorder characterized by multiple physical (motor) tics and at least one vocal (phonic) tic. We recently found levels of gamma-aminobutyric acid (GABA) to be decreased in adolescents with TD compared to healthy controls (HC). Here, we extend these findings to examine the role of oxidative stress in TD, indexed via glutathione (GSH), the major antioxidant of the brain. Using proton magnetic resonance spectroscopy (¹H MRS), we measured occipital (OCC) levels of GSH in subjects with TD and HC. We hypothesized that patients with TD would have significantly decreased levels of GSH relative to HC.

Methods: The patient population consisted of 7 TD and 13 HC subjects, ages 12-29. Subjects were diagnosed with TD via the K-SADS-PL and severity of tics was assessed by the Yale Global Tic Severity Scale (YGTSS). All participants had negative day-of-scan urine toxicology, and the TD group had YGTSS scores > 10.

In Vivo brain GSH measurement by ¹H MRS was obtained using the volume-selective J-editing difference method. Specifically, we used a standard PRESS sequence augmented with frequency-selective Shinnar-Le Roux J-editing pulses on alternate scans, with TE = 68 ms, to invert the GSH cysteinyl β doublet resonance at 2.9 ppm on every other scan; these were then subtracted to yield the GSH resonance. This process is demonstrated in Figure 1. GSH levels were represented as the ratio of the GSH to water (w) signals.

Results: As hypothesized, subjects with TD had significantly decreased OCC GSH compared to HC (2.18±0.53 x 10⁻⁷ vs. 2.83±0.64 x 10⁻⁷, p = 0.03). Results are shown in Figure 2.

Conclusions: These findings support a role for oxidative stress in TD and are consistent with the reported effectiveness of antioxidant treatments such as N-Acetylcysteine in the treatment of related disorders. Future studies in larger populations and investigating specific TD symptoms appear warranted.

Learning Objectives:
- Understand how oxidative stress may play a role in TD
- Learn about ¹H MRS as a tool to assess brain GSH in vivo

Literature References:

CARDIOVASCULAR RISK FACTORS IN INDIVIDUALS WITH BIPOLAR II DISORDER

Holly A. Swartz¹, MD, Paola Rucci¹, David J. Kupfer¹, MD, Ellen Frank¹, PhD

¹University of Pittsburgh School of Medicine, Pittsburgh, PA; ²University of Bologna, Italy

Objectives: Epidemiologic and clinical studies have documented a clear association between Bipolar (BP) disorder and cardiovascular risk factors, including obesity, hypertension, hyperlipidemia, and glucose dysregulation. Initially thought to be a consequence of medications and unhealthy lifestyles, recent studies have suggested that alterations in inflammatory and oxidative pathways may predispose individuals to these diseases, independent of external factors (1). BP II disorder, previously considered a less severe form of BP I disorder, is now recognized as a distinct phenotype characterized by high levels of impairment in multiple domains (2). Elevated cardiovascular risk factors have been well-characterized in individuals with BP I disorder; it is unclear whether individuals with BP II disorder have similar cardiovascular risk profiles to those with BP I disorder.

Methods: 501 participants (357 BP I, 144 BP II) enrolled in a clinical research program were included in these analyses. Linear regression was used to compare weight, blood pressure, lipids, and glucose between participants with BP I and II disorder, controlling for the effects of nicotine use, gender, marital status, income, CGI severity score, psychiatric comorbidity, and current medications (atypical antipsychotic medications, antihypertensive medications).

Results: Mean BMI differed between the groups: for BP I, BMI (±SD) = 31.6 (±7.3) and for BP II, BMI = 28.1 (±7.6) (p <0.05). In linear regressions, there was no significant difference between BP I and II disorder for any independent variable.

Conclusions: Mean BMI in the BP I and II cohorts were in the obese and overweight ranges, respectively. No other differences were found. Similarity in cardiovascular risk profiles between BP I and BP II groups suggests that the need for interventions to monitor and modify cardiovascular risk in individuals with BP II disorder.

Learning Objectives:
- To increase understanding of cardiovascular risk factors in bipolar (BP) II disorder
- To explore rationale for developing interventions to modify cardiovascular risk in BP II disorder

Literature References:
WHY DO SOME DEPRESSED OUTPATIENTS WHO ARE IN REMISSION ACCORDING TO THE HAMILTON DEPRESSION RATING SCALE NOT CONSIDER THEMSELVES TO BE IN REMISSION?

Mark Zimmerman, MD, Jennifer Martinez, BS, Naureen Attihullah, MD, Michael Friedman, MD, Cristina Toba, MD, Daniela Boerescu, MD
Rhode Island Hospital, Providence, RI

Objective: In treatment studies of depression remission is typically defined narrowly—based on scores on symptom severity scales. Patients treated in clinical practice, however, define the concept of remission more broadly and consider functional status, coping ability, and life satisfaction as important indicators of remission status. In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project, we examined how many depressed patients in ongoing treatment who scored in the remission range on the 17-item Hamilton Depression Rating scale (HAM-D) did not consider themselves to be in remission from their depression. Among the HAMD remitters, we compared the demographic and clinical characteristics of patients who did and did not consider themselves to be in remission.

Methods: From March, 2009 to July, 2010 we interviewed 274 psychiatric outpatients diagnosed with DSM-IV major depressive disorder who were in ongoing treatment. The patients completed measures of depressive and anxious symptoms, psychosocial functioning, and quality of life.

Results: Approximately half of the patients scoring 7 and below on the HAMD did not consider themselves to be in remission. The self-described remitters had significantly lower levels of depression and anxiety than the patients who did not consider themselves to be in remission (P < .001). Compared to patients who did not consider themselves to be in remission, the remitters reported significantly better quality of life (P < .001) and less functional impairment due to depression (P < .001). Remitters were significantly less likely to report dissatisfaction in their mental health (P < .01), had higher positive mental health scores (P < .001), and reported better coping ability (P < .001).

Discussion: Some patients who meet symptom-based definitions of remission nonetheless experience low levels of symptoms or functional impairment or deficits in coping ability thereby warranting a modification in treatment. The findings raise caution in relying exclusively on symptom-based definitions of remission to guide treatment decision-making in clinical practice.

Learning Objectives:
- Understand that many patients scoring in the remission range on the Hamilton Depression Rating Scale do not consider themselves to be in remission.
- Understand that remission should be defined in broader terms than symptom level.

Literature References:

HOW SIMILAR ARE PATIENTS WHO PARTICIPATE IN RANDOMIZED CONTROLLED TRIALS FROM THOSE WHO DON’T?

Alisa B. Busch1, MD, Yulei He2, PhD, Katya Zelevensky2, Other, Allistair J. O’Malley3, PhD
1McLean Hospital/Harvard Medical School, Belmont, MA, Department of Health Care Policy, Harvard Medical School, Boston, MA

Purpose: Most RCTs are conducted on highly selective patients, leading to questions of their generalizability for usual care populations. This study examined whether characteristics differ between those who participated in a RCT from those who did not, in the multi-site Systematic Treatment Enhancing Program for Bipolar Disorder (STEP-BD), conducted 1999-2004.

Methods: In STEP-BD, observational study arm patients could be selected into a RCT. We estimated the odds that a patient was enrolled in the Acute Depression pharmacotherapy RCT (AD-RCT) by fitting logistic regression models to all STEP-BD participants with acute bipolar depression (N=1,897). Explanatory variables included demographics, clinical information and study site. We assessed the extent that site determines RCT participation using area under the ROC curve (AUC).

Results: 308 patients participated in the RCT; while 1,589 only participated in the observational arm. Characteristics associated with RCT participation were any insurance, moderate/severe past week Global Assessment of Function, and site. Site was the most significant predictor of RCT enrollment; substantially and significantly increasing AUC (site not in model AUC=65.95%[CI:62.69]; site in model as random effect AUC=74.17%[71.77]).

Importance: Few clinical or demographic differences existed between AD-RCT participants and those in the acutely depressed observational arm. Site was an important predictor of RCT participation. Future study needs to examine site characteristics associated with RCT participation, whether these characteristics are associated with patient outcomes, and test these findings in usual care settings. These findings also are relevant for comparative effectiveness research aiming to inform healthcare decisions and policy.

Learning Objectives:
- Identify patient characteristics associated with STEP-BD randomized clinical trial (RCT) participation.
- Learn how the receiver operating characteristic (ROC) curve can be used to examine the effect size of clinical site on participation in a multi-site RCT.

Literature References:
- Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29-36.
PNB02: A BENEFICIAL TREATMENT FOR INSUFFICIENT RESPONSE WITH SINGLE AGENT TREATMENT IN SCHIZOPHRENIA?

Erik Buntinx¹, MD, Ludo Haazen¹, MD, Didier de Chaffoy², PhD, Philip D. Harvey², PhD

¹PharmaNeuroBoost NV, Alken, Belgium, ²University of Miami, Miami, FL

Efficacy of schizophrenia treatment is often hampered as severe adverse events (AE) can occur when doses of antipsychotic drugs are titrated upwards. To reach the necessary efficacy, psychiatrists often combine various typical and atypical antipsychotics, though safety and efficacy of this approach is not evidence-based (Nasallah, 2010; Barnes & Patton, 2011). Use of clozapine (CLO), although more effective is limited due to the risk for severe AE and high follow-up costs.

Therefore, an antipsychotic agent with an efficacy comparable to CLO and a potentially better AE profile compared to atypical antipsychotics would satisfy a major unmet medical need and represent a breakthrough. Such agent should ideally have a receptor binding profile similar to that responsible for the superior efficacy of CLO (central 5-HT2A blockade and D4 blockade over D2 blockade;Goodman & Gilman, 11th ed.), without binding to those receptors responsible for its AE.

This pharmacological concept could be realized by combining the receptor binding profiles of risperidone (RIS)/paliperidone (PAl) (central 5-HT2A and D2 blockade) and pipamperone (Pip) (highly selective, combined 5-HT2A and D4 antagonist (Leyesen et al., 1998)). PNB02 is a novel pharmacological agent which, by combining low doses of Pip (15 mg/d) with the lowest effective dose of RIS or PAl is expected to significantly block central 5-HT2A and D4 receptors in combination with a moderate D2 blocking, thereby mimicking the pharmacology of CLO without affecting those receptors responsible for its AE.

Study results so far confirm PNB02’s potential selective nature, absence of drug interactions between constituent agents and a comparable receptor binding profile to CLO (Data on file).

A phase I/IIa multicenter DB RCT in 60 chronic schizophrenic or schizoaffective patients stabilized with long-acting (LA) RIS/PAl but with residual psychotic symptoms is ongoing. Objectives are to explore the effect on FMR1 of adding single dose Pip, and to assess clinical outcome over 6 weeks of treatment with Pip + LA RIS/PAl vs. LA RIS/PAl alone.

Above data suggest PNB02 could have an efficacy comparable to CLO. PNB02’s constituent elements have been extensively studied and are expected to cause only moderate side-effects. PNB02 is therefore of potential value for schizophrenia patients insufficiently responding to single agent treatment and could represent a safe and effective alternative to poly-pharmacy.

Pre-clinical, phase I and PK/PD modeling data will be presented, as well as the rationale and design of the phase I/IIa Proof of Concept program aiming to demonstrate beneficial effects in schizophrenic patients suffering from residual symptoms.

Learning Objectives:
- Gain insight into current treatment of schizophrenia and its shortcomings
- Understand how PNB, through innovate drug design based on complementary receptor binding profiles of different agents develops novel therapeutic concepts
- Understand why PNB02 could be a beneficial treatment in case of insufficient response with single agent treatment
- Understand study results and research strategy for PNB02

NOVEL DOPAMINE STABILIZER

Marc Cantillon, MD, Sarath Kanekal, PhD, Mike Li, PhD, Grace Li, PhD, Robert Ings, PhD, Kouacou Adley, PhD, Laxminaran Bhat, PhD

Reviva, San Jose, CA

Funding: Reviva

Dopamine Stabilizer RP 5063 Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD)

Background: RP5063, a new atypical antipsychotic with partial agonist activity at D2, partial agonist activity at 5-HT1A, and antagonist activity at 5-HT2A receptors is a Dopamine-Serotonin System Stabilizer being developed for treating schizophrenia. It has high affinity to D2S, D2L, D3, D4, 5-HT1A, 5-HT2A, 5-HT2C, and 5-HT1 receptors. It has moderate affinity for a 1B, D1, D5, 5-HT7, and SERT receptors with no significant affinity for 5-HT3, 5-HT1B, H3, M3, AChE and NMDA receptors. RP5063 has no cardiovascular, pulmonary or CNS (other than exaggerated pharmacology) adverse effects in the safety pharmacology studies. RP5063 does not alter QT interval. Phase I randomized placebo and single/multiple dose in 55 subjects results showed excellent safety and tolerability with expected adverse effect profile.

Methods: A randomized placebo controlled Phase 1 study PK and PD of multiple, ascending oral doses of RP5063 in 32 in-patients with stable schizophrenia: 10, 20, 50 and 100 mg/day for 10 days.

Results: AEs included constipation, dizziness, emesis, insomnia and EPS including akathisia. No safety signals were identified in the clinical laboratory including prolactin and metabolic syndrome indices, vital signs, or ECG. PK was predictable, T ½ = 59 - 72 h. ANCOVA with baseline as covariate was used to compare groups, based on the five Marder PANSS factors. There was an overall effect for treatment vs. Placebo for the Positive Factor Score (p = 0.007). Moreover, repeated measures analysis revealed a reduction in the Treatment group across time (p = 0.038) and after controlling for baseline scores p = 0.027. For baseline PANSS >50, repeated measures analysis revealed a significant difference in the Treatment group across time (p = 0.005) and after controlling for baseline scores (p = 0.004). There were trends in worsening anxiety/depression and impulsivity/hostility in the placebo group. Cognitive improvement signals at certain timepoints were seen in Trials A and DSS.

Conclusions: RP5063’s unique pharmacological profile, combined with a favourable safety profile and efficacy signal in a small short study may offer significant advantage over existing treatments for schizophrenia.


Learning Objectives:
- To consider translational component of RP 5063 receptor activity
- To evaluate early clinical data on novel antipsychotic
NOP AGONISM: A NOVEL MECHANISM FOR THE TREATMENT OF ANXIETY AND DEPRESSION

Carla M. Canusa, MD, James Hutchison, PhD, Prasam Manitiptikul, PhD, John A. Moyer, PhD

Janssen Research & Development LLC, Titusville, NJ

JNJ-XXX is a novel, centrally active, potent and selective, nociceptin/orphanin-FQ peptide (NOP) receptor agonist. It has shown anxiolytic and antidepressant activity in numerous animal models. Several of these studies suggest an inverted U-shaped dose-response curve. 5 clinical studies evaluated the safety/tolerability (S/T), pharmacokinetics (PK) and pharmacodynamics (PD) of single and multiple oral doses in healthy adults. This presentation reviews results from 2 studies, with emphasis on PD effects.

Study 1: Randomized, DB, pbo-controlled, single-dose study exploring effects of JNJ-XXX on rCMglu using [18F] FDG PET, and assessing the S/T and PK of single oral doses of 50mg and 125mg in healthy males. Whilenot the 50mg nor 125mg dose showed statistically significant changes in mean rCMglu in the hypotalamus, amygdala, or hippocampus compared to pbo, consistency was observed with regard to regions of effect between Day 1 vs Day-1 and Day 2 vs Day-1 in the 50mg group, but not in the pbo or 125mg groups. There appeared to be an inverted U-shaped dose-response curve for glucose metabolism in the hypothalamus based on statistical parametric mapping analyses, as the effect was observed in the 50mg group but not the pbo or 125mg groups.

Study 2: A two-part, DB, pbo-controlled single (part 1) and multiple (part 2) dose study evaluating effects of JNJ-XXX on CCK-4 induced anxiety. S/T and PK in healthy males. Part 1 had 2 cohorts: one randomized to 50mg (n=12) or pbo (n=6) and the other randomized to 125mg (n=12) or pbo (n=6). In part 2, 36 subjects were randomized to 50mg, 125mg or pbo. In part 1 CCK4 50 μg iv was given the day following the dose of JNJ-XXX, and after 7 days of treatment in part 2. Anxiety was measured before and after CCK-4 dosing with the Spielberger State Anxiety Inventory (SSAI) and Total Panic Symptom Score (TPSS), respectively. In part 1, no differences were seen on SSAI for either dose cohort vs pbo. The LS mean (SE) difference on TPSS in 50mg cohort vs pbo was -3.7 (2.9) (at alpha=0.1, one-sided level, p=0.1097); in the 125mg cohort LS mean difference was 5.2 (3.4), favoring pbo. In part 2, SSAI was also significantly lower (p=0.0565) in the 50mg group vs pbo, but not in the 125mg group. There was no difference between both treatment groups and pbo on TPSS.

PK and S/T results were consistent across both studies. All subjects receiving JNJ-XXX showed systemic exposure, with median t1/2 occurring at 1-6 hrs. Steady state was not achieved in either study. Most AEs were mild; G-related effects were reported most commonly (up to 38%).

PD results from these two studies suggesting an inverted U-shaped are consistent with preclinical data, and inform dosing for future trials of JNJ-19385899 to further understand the utility of NOP agonism in the treatment of anxiety and depression.

Learning Objectives:
- Demonstration of PD studies informing dosing
- Explore potential of NOP agonist in the treatment of anxiety and depression

EARLY CLINICAL DEVELOPMENT OF THE OPIOID MODULATOR ALKS 5461 IN THE TREATMENT OF DEPRESSION AND ADDICTION

Elliot W. Ehrich, MD, Ryan Z. Turncliff, PhD, Edward M. Sellers, MD, PhD, Reese T. Jones, MD, Maurizio Favata, MD

'Alkermes PLC, Waltham, MA, 'DL Global Partners, Toronto, ON, Canada, UC San Francisco, San Francisco, CA, 'Mass General Hosp, Boston, MA

The endogenous opioid system is thought to play a key role in the regulation of mood. Indeed, the ‘opium cure’ was a pharmacologic mainstay of depression therapy prior to the advent of the tricyclic and monoamine oxidase inhibitor anti-depressants in the 1950’s. The precise mechanism of endogenous opioids in mood regulation, however, is uncertain.

The contemporary use of opioids for depression is limited by abuse potential presumably a result of mu opioid agonism. ALKS 5461 consists of buprenorphine (BUP), a partial mu agonist, combined with ALKS 33, a counter-acting mu antagonist, co-formulated in a sublingual dosage form. The ALKS 33 component was designed to be minimally metabolized, highly potent, and sublingually bioavailable with the latter two properties being essential for sublingual co-formulation.

Initial clinical study of ALKS 33 included a remifentanil challenge protocol in opioid-experienced volunteers. Oral 10 and 20 mg doses of ALKS 33 completely blocked mu agonist effects of serial pulses of remifentanil as assessed by physiologic (pupilometry) and subjective VAS assessments (drug liking, high, etc.). Duration of blockade was >24 h following a single dose. Subsequently, a drug-drug interaction study was performed evaluating escalating doses of sublingual ALKS 33 co-administered with 8 mg BUP in a blinded fashion. In this study, 1 mg ALKS 33 caused a partial attenuation of mu effects whereas doses ≥4 mg yielded complete blockade.

A double-blind placebo controlled pilot study of once-daily sublingual ALKS 5461 was conducted in 32 patients with treatment resistant depression (TRD). Two dose ratios of BUP: ALKS 33 were evaluated: an 8:1 ratio (partial blockade of BUP mu agonist effects) and a 1:1 ratio (complete blockade). Efficacy was measured using the HAM-D-17 and the MADRS. Evidence of rapid efficacy was observed with both dose ratios at 7 days, with greatest efficacy at the 1:1 ratio, i.e. with complete mu blockade (p=0.032 and p=0.054; 1:1 ratio vs. placebo for HAM-D-17 and MADRS, respectively). ALKS 5461 was generally well tolerated.

The most common AEs were dizziness, nausea, vomiting, and sedation, which occurred more frequently with the 8:1 ratio.

ALKS 5461 may represent a novel treatment for depression with a rapid onset. A larger phase II study is ongoing. Perturbation of the endogenous opioid system has also been linked to the development and propagation of addictive disorders. An ALKS 5461 – cocaine interaction study is ongoing.

Acknowledgement: Work funded in part by NIDA

Learning Objectives:
- Understand the therapeutic potential of combining counter-acting opioid receptor modulators for TRD and other disorders
- Understand the potential role of opioids in the regulation of mood
CLINICAL DEVELOPMENT OF THE NOREPINEPHRINE REUPTAKE INHIBITOR EDIVOXETINE (LY2216684 HCL) FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: USE OF PHARMACOKINETICS, PHARMACODYNAMICS AND BIOMARKERS

William Kielbasia\textsuperscript{1}, PhD, Tonya Quinlan\textsuperscript{1}, BS, Debra Luffer-Atlas\textsuperscript{1}, PhD, Malcolm I. Mitchell\textsuperscript{2}, Eshetu Wondmagegnehu\textsuperscript{1}, PhD, Michael A. Turi\textsuperscript{1}, MD, Mary Anne Dell\textsuperscript{3}, MS, Sanjay Dubeh\textsuperscript{1}, MD, Celine Goldberger\textsuperscript{1}, MD

\textsuperscript{1}Eli Lilly and Company, Indianapolis, IN, Lilly Research Centre, Surrey, United Kingdom

Current treatment recommendations for major depressive disorder (MDD) focus on selective serotonin reuptake inhibitors (SSRIs) as a first-line treatment. While SSRIs have demonstrated efficacy, response to treatment is varied with approximately only one-third of patients meeting criteria for remission. Symptoms of depression may also involve dysregulation of noradrenergic neurotransmission. Edivoxetine (2-Morpholinemethanol, \(-\alpha\)/[[5-fluoro-2-methoxyphenyl]methyl]-(tetrahydro-2H-pyran-4-yl]-, hydrochloride, \(\alpha R, 2S\)) is a potent inhibitor of the norepinephrine transporter. Phase 1 studies were conducted to characterize edivoxetine pharmacokinetics (PK) and pharmacodynamics (PD). In a PK drug interaction study in healthy adults, paroxetine mildly increased the exposure of edivoxetine, presumably due to chemical inhibition of the cytochrome P450 (CYP) 2D6 enzyme, suggesting that CYP2D6 is partly involved in the metabolism of edivoxetine. However, edivoxetine appears to depend less on the CYP2D6 enzyme for metabolism than atomoxetine and is likely to have less exposure variability in patients with diverse CYP2D6 polymorphism. Peripheral (plasma) and central (cerebrospinal fluid, CSF) NET inhibition using 3,4-dihydroxyphenylglycol (DHPG) as a biomarker of pharmacologic activity was evaluated to inform edivoxetine dose selection for efficacy trials. In healthy adults, edivoxetine decreased plasma and CSF DHPG concentrations suggestive of NET inhibition. Based on PK/PD modeling and simulation, a nonlinear dose – effect relationship for plasma and CSF DHPG was revealed; however, higher edivoxetine doses led to a greater reduction from baseline of CSF DHPG (\(\text{IC}_{50,\text{CSF}} = 75\%\)) compared to plasma DHPG (\(\text{IC}_{50,\text{CSF}} = 35\%\)). The dissimilar effects on peripheral and central DHPG suggest that CSF DHPG might be a more sensitive and representative biomarker for central target engagement than plasma DHPG. The PK/PD model provided insights about edivoxetine pharmacology and may serve as a relevant predictor of an effective dose. A dose range of 6 – 18 mg investigated the efficacy of edivoxetine in MDD as monotherapy and adjunctive treatment to a SSRI. In both studies, edivoxetine was generally well-tolerated and demonstrated the potential to be an effective drug to treat MDD.

Learning Objectives:
\begin{itemize}
  \item To present how PK was used to inform clinical development of edivoxetine.
  \item To present how PD was used to inform clinical development of edivoxetine.
  \item To present how biomarkers were used to inform clinical development of edivoxetine.
\end{itemize}

MERCK NEUROSCIENCE PHARMACEUTICAL PIPELINE: JUNE 2012

David Michelson\textsuperscript{1}, MD, Armin Szegedi\textsuperscript{1}, MD, PhD

\textsuperscript{1}Merck & Company, North Wales, PA, \textsuperscript{2}Merck Research Laboratories, Rahway, NJ

Merck is focused on several disease areas within neuroscience, and two molecules of interest currently in clinical development are MK-8931, a BACE inhibitor being studied as a potential treatment for Alzheimer’s Disease, and MK-4305, an orexin receptor being studied for insomnia. A body of new data has provided information about these novel mechanisms, and about their potential value as therapeutics, which will be discussed in this 10 minute presentation.

Learning Objectives:
\begin{itemize}
  \item Attendees will learn about a novel intervention in the amyloid pathway being investigated for Alzheimer’s disease.
  \item Attendees will learn about the potential of orexin receptor antagonism as a treatment for insomnia.
\end{itemize}
A NOVEL V1A RECEPTOR ANTAGONIST AND POTENTIAL ANTIDEPRESSANT, SRX246, BLOCKS VASOPRESSIN MEDIATED EFFECTS ON STRESS & FEAR: AN FMRI STUDY

Neal G. Simon1,2, PhD, Royce Lee1, MD, Michael J. Brownstein1, MD, PhD, Emil Coccoaro1, MD
1Azevan Pharmaceuticals, Inc, Bethlehem, PA; 2Lehigh University, Bethlehem, PA; 3University of Chicago, Chicago, IL

Background: SRX246 is a novel vasopressin 1a receptor antagonist that is efficacious in animal models of depression and other stress-related disorders. The drug has completed Phase I Single Ascending Dose (SAD) and 14-day Multiple Ascending Dose (MAD) Clinical Trials with excellent safety, tolerability, and pharmacokinetics.

Purpose: Use fMRI to determine if orally administered SRX246 can block the effects of intranasally administered vasopressin (AVP) on the brain response to threatening emotional stimuli in healthy volunteers. Previous studies have shown effects of AVP signaling on the amygdala and other brain structures involved in the neural processing of social and emotional cues, including the temporoparietal junction, subgenual cingulate, and connected structures. Reactivity to stimuli such as emotional faces in these brain regions has been linked to major depressive disorder.

Method: All study procedures were approved by the Institutional Review Board of The University of Chicago. The subjects (n=29 males aged 18-55) provided informed consent and met the inclusion criteria. A baseline fMRI scan was acquired before randomization to oral SRX246 (120mg PO BID; n=15) or placebo (n=14) for 5-10 days, after which subjects returned for a second scanning session. At Session 2, subjects within the SRX246 and placebo groups were randomized again to either intranasal vasopressin (Pitressin 40 IU) or placebo. The implicit processing of emotional facial expressions (Ekman faces; Angry, Neutral, Happy) was tested while fMRI data were acquired.

Results: SRX246 treatment (120 mg PO BID) significantly blunted the increased BOLD signal seen in response to angry faces following intranasal vasopressin in the right temporoparietal cortex, specifically Brodmann Area 39. SRX246 treatment also significantly blunted the BOLD signal to angry faces in the medial prefrontal cortex, including the anterior cingulate cortex, in comparison to placebo treatment.

Conclusion: These findings demonstrate that amplification of circuit function by vasopressin during task performance is blunted by SRX246, showing that the drug enters brain and acts on vasopressin receptors. SRX246 blunted effects of intranasal vasopressin on BOLD signal change in response to angry faces in the amygdala, temporoparietal cortex, and anterior cingulate. These data provide proof-of-mechanism for SRX246 and also indicate potential novel actions the compound on regional brain reactivity to social and emotional stimuli highly relevant to major depressive disorder.

Financial Support: NIH Award MH-063663 and Azevan Pharmaceuticals, Inc.

Learning Objectives:
- Enhance knowledge of vasopressin receptor antagonist effects in the brain
- Understand a novel approach to studying new vasopressin modulates neural responses to emotional stimuli
- Assess the potential utility of a novel antidepressant using fMRI

TRANSLATIONAL EVALUATION OF JNJ-18038683, A SELECTIVE 5-HT7 RECEPTOR ANTAGONIST IN DEPRESSION

Jaskaran Singh1, MD, Michelle Kramer1, MD, Christine Dugovic2, PhD, Nicholas Carruthers3, PhD, De Boer Peter1, PhD, Pascal Bonaventure4, PhD, Timothy Lovenberg5, PhD, Maurizio Favà6, MD
1Janssen R&D, Titusville, New Jersey, 2Johnson and Johnson, Tokyo, Japan, 3Janssen R&D, La Jolla, CA, 4Janssen R&D, Beerse, Belgium, 5Massachusetts General Hospital, Boston, MA

5-HT, receptor blockade has been shown to be effective in rodent models of depression and to increase the latency to REM sleep and decrease REM duration. JNJ-18038683 is a selective 5HT7 receptor antagonist. JNJ-18038683 displaced, with high affinity, specific [H]5-HT binding sites and produced a concentration dependent decrease of serotonin-stimulated adenyl cyclase from rat and human 5-HT receptors expressed in HEK293 cells. In rodents, JNJ-18038683 increased the latency to REM sleep and decreased REM duration which is maintained with multiple administrations. The compound was effective in a behavioral model of helplessness such as the mouse tail suspension test. In healthy human volunteers, JNJ-18038683 was found to increase REM latency and to decrease REM sleep duration demonstrating that the effect of 5-HT, blockade on REM sleep translated from rodent to humans. Like in rats, JNJ-18038683 was also found to enhance REM sleep suppression induced by citalopram in humans, although a drug-drug interaction could not be ruled out. In a double blind, active- and placebo-controlled randomized clinical study in patients suffering from depression, neither treatment with pharmacologically active doses of JNJ-18038683 nor citalopram separated from placebo, indicating a failed study lacking assay sensitivity. A post hoc analyses using an enrichment window strategy, where all the efficacy data from sites with an implausibly high placebo response (MADRS <= 12 at endpoint) and from sites with no placebo response (<10% improvement; MADRS >=28) are censored, there was a clinically meaningful and statistically significant difference between JNJ-18038683 and placebo. The preclinical and clinical data are suggestive of antidepressant efficacy of JNJ-18038683 and required further studies to characterize its potential antidepressant efficacy.

Learning Objectives:
- Role of 5HT7 in sleep and depression
- Translational development of a new antidepressant
- Site based enrichment analyses
PANEL OVERVIEW:
IDENTIFYING COMMON TARGETS IN TREATING IMPULSE CONTROL DISORDERS
Lorrin Koran†, MD, Jon Grant†, MD, Emil Coccaro², MD, Susan McElroy³, MD
†Stanford University, ‡University of Minnesota, §University of Chicago, Lindner Center of HOPE

Purpose: To identify potential neurotransmitter and intra-neuronal physiological targets for pharmacotherapies across DSM-IV-TR impulse control disorders.

Content: The panel will review treatment outcome evidence from controlled and uncontrolled pharmacotherapy trials for pathological gambling (PG), intermittent explosive disorder (IED), trichotillomania (TTM) and skin picking disorder (SPD) to highlight commonalities and differences in the neurophysiological systems primarily targeted by effective and possibly effective drugs.

Methodology: Pharmacotherapy studies and integrative reviews for these impulse control disorders have been identified by searching MEDLINE and the results examined for suggested shared and non-shared mechanisms of action.

Results: Serotonergic drugs have demonstrated efficacy in IED and mixed efficacy in PG and SPD. But are ineffective in TTM. Opioidergic and glutamatergic-modulating drugs are effective in PG (naltrexone, nacetylcysteine, possibly topiramate) and TTM (naltrexone and nacetylcysteine), possibly effective in skin picking (lamotrigine, possibly naltrexone), but perhaps not in IED (where carbamazepine and oxcarbazepine are possibly effective). Atypical antipsychotic drugs, with their complex effects on neurotransmission, may be effective in TTM, but show little promise in PG. Lithium, affecting serotonergic neurotransmission and intra-neuronal signaling systems, is possibly effective in PG in subjects with bipolar features and in TTM.

Importance for advancing the field: Because these drugs have more than one neurophysiological effect, clear attribution of their clinical efficacy to the mechanisms mentioned is not possible. The impulse control disorders, singly and together, display heterogeneity (e.g., in gender distribution and in comorbid conditions). Still, clarifying neurotransmission and other neuronal processes that may characterize drugs that alleviate these life-imparing conditions is sorely needed.

Literature References:
PHARMACOTHERAPY TARGETS IN INTERMITTENT EXPLOSIVE DISORDER

Emil F. Coccaro, MD
University of Chicago, Chicago, IL

Intermittent Explosive Disorder (IED) affects about 5% of the US population over the lifetime and nearly 3% in any given year. While there are no FDA approved treatments for IED a number of agents can be used for treating impulsive aggressive behavior. This includes SSRI s, various anticonvulsants, and other agents. This presentation will review the biology of impulsive aggression and IED and will review the current state of treatment options for this disorder. New data regarding the possible role of peptides such as Neuropeptide Y and Substance P will be reviewed as possible new targets for treatment options. In addition, we will review methodological issues regarding the nature of clinical trials for IED.

Learning Objectives:
- Summarize pharmacotherapies for IED.
- Suggest new clinical trials and new drug development pathways.

Literature References:

PHARMACOTHERAPY TARGETS IN TRICHOTILLOMANIA AND SKIN PICKING DISORDER

Lorin M. Koran MD
Stanford University, Stanford, CA

Trichotillomania (TTM) can devastate a life. A 12-week randomized, double-blind trial (RCT) (n=50) reported 56% of n-acetylcysteine (NAC) subjects were much or very much improved vs. 16% of placebo subjects. An olanzapine RCT was also positive. Small controlled trials have found SSRIs no better than placebo. Open trials of an SNRI (venlafaxine), an anticonvulsant (topiramate), and naltrexone report positive outcomes. Thus, drugs that modulate extracellular glutamate concentration in the nucleus accumbens (like NAC), block D2 receptors (like olanzapine), and possibly drugs that share mechanisms with SNRIs, topiramate or naltrexone deserve further study in TTM.

Skin picking disorder (SPD) carries risks of infection and scarring and may cause marked dysfunction. An RCT and a double-blind, placebo-controlled discontinuation trial suggest fluoxetine’s efficacy, but a citalopram RCT was negative. Open trials of SSRIs have been positive. A positive open trial of lamotrigine, which decreases glutamatergic stimulation in the nucleus accumbens, was not confirmed in an RCT. Case reports support using atypical antipsychotic medications, either alone or as adjunctive treatment, and naltrexone, an opioidergic drug that modulates dopamine transmission in the ventral tegmental area-nucleus accumbens pathway.

Future TTM and SPD treatment studies should utilize larger samples, longer treatment/follow-up periods, measures of biological heterogeneity (e.g., genetic markers, neuropsychological measures, fMRI) and examine possible clinical subtypes to speed discovery of treatments for these painful, disruptive disorders.

Learning Objectives:
- Summarize pharmacotherapies for TTM and SPD.
- Suggest new clinical trials and new drug development pathways.

Literature References:
PANEL OVERVIEW:
EMERGING CLINICAL EVIDENCE ON OXYTOCIN IN SCHIZOPHRENIA

Deanna Kelly, PharmD, Bruno Averbeck, PhD, David Feifel, MD, Cort Pedersen, MD, Leah Rubin, MD, Mary Lee, MD

1University of Maryland, Baltimore, 2NIH, 3University of California, San Diego, 4University of North Carolina at Chapel Hill, 5University of Illinois at Chicago, 6NIDA

Oxytocin is a neuropeptide associated with a wide variety of social behaviors in diverse species. Interest in the intranasal use of this neuropeptide has rapidly expanded over the past 5 years in a variety of psychiatric disorders. Schizophrenia is a disorder that associated with a spectrum of social and emotional deficits such as impaired perception of emotions, impaired social cue perception and biased reasoning about certain types of social information. It is also a thought disorder associated with anxiety and mistrust. Difficulty initiating prosocial and social behaviors may be in part due to positive, negative, social cognitive deficits and anxiety. In the past year published studies on oxytocin in schizophrenia have become available.

We are presenting a symposium on the most recent emerging clinical data of oxytocin in schizophrenia. Dr. Bruno Averbeck will be presenting the results on the effects of intranasal oxytocin on emotion recognition. In his study oxytocin improved the ability of schizophrenia to recognize emotions in a single dose challenge. In parallel, 2 clinical trials have recently been published by Dr. David Feifel (3 week trial, N=15) and colleagues and Dr. Cort Pederson and his team (2 week trial, N=25). Dr. Feifel and Dr. Pederson will present their findings together in the symposium based on the primary outcomes of interest. Dr. Feifel will begin by sharing the clinical trials results from both studies on the effects of intranasal oxytocin on core symptoms in schizophrenia, both positive and negative symptoms. Dr. Pederson will follow with a presentation on intranasal oxytocin and its effects of intranasal oxytocin on social cognitive measures and neurocognition in schizophrenia. Following these discussions, Dr. Leah Rubin will present on the influence of sex, sex steroid hormone fluctuations, and peripheral oxytocin levels on clinical symptoms and emotional processing in men and women with schizophrenia. Finally, Dr. Mary Lee will present a recently completed randomized placebo controlled double blind clinical trial (projected N=30, 3 week) and discuss the symposium. Dr. Deanna Kelly also a coinvestigator will moderate and chair the session.

Learning Objectives:
- The participant should understand the clinical data on oxytocin on emotion recognition and social cognition in schizophrenia
- The participant will examine the data from 3 clinical trials on intranasal oxytocin in schizophrenia and the effects on psychiatric symptoms

OXYTOCIN IMPROVES EMOTION RECOGNITION IN PATIENTS WITH SCHIZOPHRENIA

Bruno Averbeck, PhD
NIH, Bethesda, MD

Background: Impairments in social functioning are common in schizophrenia. Numerous studies have shown impaired perception of emotional expressions in schizophrenia and unaffected first-degree relatives also seem to be impaired, albeit to a lesser extent. In the current experiments we hypothesized that (1) patients with schizophrenia would have a deficit relative to a control group on recognizing emotions, as has previously been shown, and (2) oxytocin could ameliorate some of this deficit, as has been shown in autism spectrum disorders.

Methods: To examine emotion recognition deficits in patients and see whether oxytocin could improve these deficits, we carried out two experiments. In the first experiment we recruited 30 patients with schizophrenia and 29 age and IQ matched control subjects, and gave them an emotion recognition task. Following this, we carried out a second experiment in which we recruited 21 patients with schizophrenia for a double blind, placebo controlled cross-over study of the effects of oxytocin on the same emotion recognition task.

Results/Discussion: In experiment 1, when the patient group was compared to the matched control group, the patients were less accurate than controls in both morphed and unmorphed conditions and the performance of both groups was worse in the morphed condition. There were main effects of group (F(1,27) = 14.41, p<0.001), emotion (F(5,285) = 40.95, p<0.001), and morphing (F(1,342) = 125.25, p<0.001). In the second experiment we examined the effects of oxytocin on emotion discrimination within a group of patients with schizophrenia. Analysis of the fraction correct data showed that oxytocin improved emotion recognition (F(1, 264) = 7.74, p = 0.006), morphing decreased performance (F(1, 322) = 22.31, p < 0.001) and different emotions were processed differently (F(5, 100) = 35.42, p < 0.001). In the final analysis we compared the performance of the patients from the second experiment on oxytocin to the performance of the control group in the first experiment, to see the effect of oxytocin on the group difference. The control group performed at 72% correct, the patient group off oxytocin in the second experiment at 54% correct and the patient group on oxytocin at 58% correct. Thus, oxytocin made up 22% of the difference in performance.

Learning Objectives:
- Understand emotion recognition deficits in schizophrenia
- Understand effect of oxytocin on emotion recognition in schizophrenia

Literature References:
INTRANASAL OXYTOCIN REDUCES CORE SYMPTOMS OF SCHIZOPHRENIA

David Feifel, MD, Cort Pedersen1, MD, Kai MacDonald1, MD, David Penn1, MD
1University of California, San Diego, CA. University of North Carolina at Chapel Hill, NC.

Converging evidence suggests that the oxytocin system may be a fruitful therapeutic target for schizophrenia. It has been well established that oxytocin strongly regulates social cognition, trust and affiliation, each of which is disturbed in schizophrenia. Dopamine and glutamate, neurotransmitters highly implicated in schizophrenia, are regulated by oxytocin and vice-versa and there is compelling evidence that the oxytocin system is dysregulated in people with this disorder. In animals, systemic administration of oxytocin produces antipsychotic-like effects, whereas disruption of the endogenous oxytocin system produces the opposite effects. Though it is believed that oxytocin has poor penetration across the blood-brain barrier from the systemic circulation, the intranasal route of administration is believed to provide a favorable pathway for peptides such as oxytocin into the CNS. Exploiting this, many investigators have shown that a single intranasal administration of oxytocin in normal subjects produces distinct immediate effects on measures of social cognition and affiliation which correspond with robust changes in regional brain activation. These findings inspired recent proof-of-concept clinical trials in patients with schizophrenia.

In one recently completed placebo-controlled, cross-over trial conducted by Dr. Feifel’s team at University of California - San Diego, intranasal oxytocin taken daily for three weeks (titrated to 48 IU BID) in addition to stable doses of antipsychotic medication significantly reduced positive and negative symptoms compared to placebo (n=15). A separate team of investigators at the University of North Carolina lead by Dr. Pedersen conducted a 14 day parallel arm study of daily intranasal oxytocin (24 IU BID, n=14) versus placebo (n=11) given adjunctive to stable regimes of antipsychotic medication in schizophrenia patients. They found within groups that oxytocin recipients had significantly greater declines in PANSS total, positive, negative and general subscale scores while the placebo group had no significant changes in these variables. ANCOVAs controlling for baseline measures showed that total PANSS scores declined significantly more in the OT compared to the placebo group. Intranasal oxytocin was well tolerated in both studies. Both studies also found oxytocin produced improvement in highly relevant secondary measures beyond positive and negative symptoms (see Pedersen et al abstract in this symposium). Together these preclinical and clinical findings suggest that there is an exciting opportunity to develop novel treatments for schizophrenia targeting oxytocin receptors. However, larger studies addressing several parametric issues are needed to both replicate these exciting initial findings and to inform possible drug development efforts.

Learning Objectives:
- Become aware of evidence supporting therapeutic effect of oxytocin in schizophrenia
- Understands the opportunities and barriers to developing oxytocin as a treatment

Literature References:

INTRANASAL OXYTOCIN TREATMENT IN SCHIZOPHRENIA: IMPROVEMENT IN SOCIAL COGNITION, PANSS SOCIAL ITEM SCORES AND VERBAL LEARNING

Cort Pedersen1, MD, David Feifel1, MD, Kai MacDonald1, David Penn1, PhD
1University of North Carolina at Chapel Hill, NC. 2University of California at San Diego, San Diego, CA.

Purpose: Because oxytocin (OT) has prosocial (Lee et al., 2009) and antipsychotic-like effects in animals (Caldwell et al., 2009; Feifel & Reza, 1999; Lee et al., 2005; 2007) we hypothesized that OT treatment would improve social cognition as well as decrease psychotic symptoms in schizophrenia.

Methods: The 1st randomized clinical trial (RCT) compared twice daily intranasal OT (24 IU/dose, N=14) vs. placebo (N=11) for 14 days on social cognition tests and PANSS scores in schizophrenia patients with baseline total PANSS scores >60 and stable antipsychotic medications and symptoms for >1 month. In the 2nd RCT, patients (N=15) with total PANSS scores >55 and stable medication regimens received twice daily intranasal OT (20 IU/dose 1st wk, 40 IU wks 2 and 3) or placebo in a crossover design with a 1 week washout period. The California Verbal Learning Test (CVLT) was administered before and after each 3-wk segment of the trial. Medications were unchanged during the trials.

Results: Demographic data, psychiatric history and baseline measures did not differ between treatment groups in either RCT. OT, but not placebo, recipients in the 1st RCT improved significantly on mean PANSS social items scores (suspicousness, hostility, passive/athetotic social withdrawal, uncooperativeness, active social withdrawal) and accurate identification of 3rd order false belief in the Bröne Theory of Mind (ToM) Test; 2) trended on the Bröne Test toward more accurate identification of 2nd order false belief and deception as well as rating faces as less untrustworthy. However, there were no group differences on changes in these measures. In the 2nd RCT, CVLT scores improved significantly in the OT compared to the placebo group on Total Recall, Short Delay Free Recall, Short Delay Cued Recall, Total Repetitions and Total Recall Discriminability. None of these measures changed significantly in the placebo group.

Significance: Enhancement of social cognition suggests that OT treatment may improve social dysfunction (Couture et al., 2006), which responds poorly to antipsychotic medications and is a major cause of disability in schizophrenia. OT improvement in neurocognition may further improve social and general functioning.

Supported by the Foundation of Hope for Research and Treatment of Mental Illness and MH093529 (CP), MH051246 (DP) and the Stanley Medical Research Institute (DF).

Learning Objectives:
- Appreciate the relationship between social dysfunction and disability in schizophrenia.
- Understand that social dysfunction in schizophrenia is related to deficits in social cognition and neurocognition
- Learn about new evidence that intranasal oxytocin treatment improves social cognition in schizophrenia.
- Learn about new evidence that intranasal oxytocin treatment improves verbal memory in schizophrenia.

Literature References:
SEX-SPECIFIC ASSOCIATIONS BETWEEN PERIPHERAL OXYTOCIN, SYMPTOMS, AND EMOTION PERCEPTION IN SCHIZOPHRENIA

Leah H. Rubin1, PhD, Sue Carter1, PhD, Lauren Drogos2, Hossein Pournajafi-Nazarloo3, MD, John A. Sweeney4, PhD, Pauline M. Maki5, PhD

1University of Illinois at Chicago, Chicago, IL, 2University of Texas Southwestern, Dallas, TX

Sex hormones are implicated in the pathogenesis of schizophrenia. Low levels of estrogen and oxytocin (OT), hormones that may act as neuromodulators, are common in women with schizophrenia, and variations in these hormones affect cognition (including social cognition) that is impaired in the disease. Emerging evidence from clinical trials suggests that oral estrogen and intranasal OT might reduce symptom severity in schizophrenia. Intranasal OT may also improve social cognition in schizophrenia. Here we investigated the influence of sex, sex steroid hormone fluctuations, and peripheral OT levels on clinical symptoms and emotional processing in schizophrenia. Fifty women (30 healthy; 20 patients) completed assessments at two distinct phases of their menstrual cycle; 54 men (27 healthy; 27 patients) completed testing at comparable intervals to the women. Assessments included the Positive and Negative Syndrome Scale and the PENN Emotion Acuity Test, a facial emotion recognition and perception task. We obtained plasma hormone assays of estrogen, progesterone, testosterone, and OT. Female patients showed less severe symptoms during the midluteal versus early follicular phase. OT did not fluctuate across phases, but in female patients, higher OT levels were associated with less severe positive, general, and overall psychopathology. In both sexes, higher OT levels were associated with more prosocial behavior. Higher OT levels also related to perceiving faces as happier in both female patients and controls but not in men. Individual differences in OT levels differentially predict clinical symptoms and emotion processing in schizophrenia. Findings suggest that endogenous OT may impact the clinical manifestation of schizophrenia. Future trials of OT should include measures of social cognition to evaluate whether exogenous OT also makes patients view faces as "happier", explore the functional correlates of this benefit, and consider sex when evaluating OT in schizophrenia.

Learning Objectives:
- To understand the effects of menstrual cycle phase and related fluctuations in peripheral hormone levels on clinical symptoms in women with schizophrenia
- To understand the influence of sex, sex steroid hormone fluctuations, and peripheral OT levels on emotional processing in schizophrenia

Literature References:
- Rubin, L.H., et al. Sex-specific associations between peripheral oxytocin and emotion perception in schizophrenia. Schizophrenia Research 2011;130: 266-270.
PANEL OVERVIEW:
NEUROIMMUNE TARGETS FOR TREATMENT OF SUBSTANCE AND ALCOHOL USE DISORDERS
Phil Skolnick, PhD, Raye Litten, PhD, Peter Grace, PhD, Robert Harris, PhD, Linda Watkins, PhD, David McCann, PhD
NIH/NIDA, National Institute on Alcohol Abuse and Alcoholism, School of Medical Sciences, University of Adelaide, University of Texas at Austin, University of Colorado at Boulder

Converging lines of evidence indicate that immune signaling in the central nervous system contributes to the pharmacological actions of commonly abused substances including alcohol, opiates, and cocaine. Among the immune signaling pathways that have been identified in the CNS, the Toll-like receptor 4 (TLR4), located in microglia, appears to play a key role in the behavioral effects of multiple abused substances. Thus, both genetic and pharmacologic evidence indicate that activation of this inflammatory TLR4 signaling pathway via MyD88 and NF-kB is crucial for the sedative and motor impairment produced by alcohol exposure. Moreover, activation of TLR4 signaling via injection of lipopolysaccharide (LPS) to mice selectively promotes alcohol consumption. Remarkably, this effect persists for at least 3 months after a single LPS treatment without changes in either taste (sweet or bitter) perception or palatability (sucrose intake). LPS does not appear to increase alcohol intake in mice lacking either a key component of TLR4 signaling (CD14 knockout mice) or the major proinflammatory cytokine IL-6 (IL6 knockout mice). Other neuroimmune components, downstream from the activation of TLR4, have also been shown to regulate alcohol consumption. Opiates also activate glial and endothelial cells through the TLR4 pathway rather than classical opiate receptors. The proinflammatory state produced by opiate-induced activation of these non-neuronal cells is now linked to many of the classical pharmacological effects associated with opiates, including tolerance, dependence, reward, and respiratory depression. Indeed, the impact of TLR4 activation extends beyond opiates, with in vivo and in vitro evidence of non-neuronal cell activation by cocaine, and blockade of several behavioral and neurochemical measures of cocaine reinforcement by TLR4 inhibition. The ability to modulate the pharmacological actions of alcohol, opiates, and cocaine through TLR4 linked pathways indicates the potential for new therapeutic avenues to treat multiple substance disorders; the identification of "unnatural" isomers of opioid derivatives (e.g. (+)-naloxone; (+)-naloxone) as selective TLR4 antagonists provides a platform to develop such therapies.

Learning Objectives:
- Understand the contribution of immune signaling in the CNS to the pharmacological actions of commonly abused substances
- Link this understanding to the potential for developing novel therapies to treat substance use disorders

ACTIVATION OF IMMUNE SIGNALING PATHWAYS IS IMPLICATED IN SOME OF THE PHARMACOLOGICAL EFFECTS OF ETHANOL
Peter M. Grace, PhD, Yue Wu, PhD, Jacob Thomas, BS, Lauren Nicotra, BS, Liang Liu, PhD, Andrew A. Somogyi, PhD, Kenner C. Rice, PhD, Linda R. Watkins, PhD, Mark R. Hutchinson, PhD
School of Medical Sciences, University of Adelaide, Adelaide, South Australia, Australia, Chem Bio Res Branch, NIDA and NIAAA, Rockville, MD, Department of Psychology & Neuroscience, & the Center for Neuroscience, Boulder, CO

In the past two decades a trickle of manuscripts examining the non-neuronal central nervous system immune consequences of exposure to drugs of abuse has now swelled to a significant body of work. Initially, these studies reported associative evidence of central nervous system proinflammation resulting from exposure to the drugs of abuse demonstrating key implications for neurotoxicity and disease progression. More recently, we have observed that the role of the TLR4-mediated drug-induced activation of central immune signaling is now understood to contribute substantially to the pharmacodynamic actions of the drugs of abuse. Of specific interest here is an evolving appreciation of the non-neuronal actions of opioids and alcohol. Evidence for opioid and alcohol activity at innate immune pattern recognition receptors, e.g. Toll-like receptor 4 (TLR4), is now available from disparate pharmacological and genetic knockout models. Critically, these data demonstrate the obligatory role of central immune signaling in the actions of alcohol and opioids. Moreover, human immunogenetic studies now implicate mutations in proinflammatory immune genes and association with alcohol and opioid dependence. Given that both opioids and alcohol have TLR activity, this also raises the possibility of a novel site for their individual behavioral effects as well as drug-drug interactions that may also contribute to their synergistic actions.

The central immune signaling system that opioids and alcohol engage have yet to be pharmacologically targeted. Owing to the clear therapeutic opportunities that pharmacology provides, our efforts have also been directed at identifying small molecules that may beneficially intervene to stop opioid- and alcohol-induced proinflammatory central immune signaling, specifically targeting the TLR4 signaling cascade. To this end, we have identified novel TLR4 activity of the opioid inactive (+) isomers of opioid antagonists such as (+)-naloxone and (+)-naloxone. The actions of these and other TLR4 targeted pharmacotherapies in combination with opioids and alcohol in behavioral and molecular assays will be presented. Preclinical experimental data will be presented from studies that examined the impact of TLR signaling on opioid and alcohol pharmacodynamics. The opioid and alcohol-induced activation of TLR4-dependent molecular signaling events and radioligand binding in TLR4 knockout (KO) and wildtype brains will also be presented to provide clear evidence of a direct receptor level site of action. Specifically, morphine analgesia, tolerance and withdrawal in wild-type (WT) mice, and KO of various components of key TLR signaling pathways, namely, KO of TLR4, TLR2, TLR4/2, MYD88, TLR9 or TLR8 were quantified. Alcohol loss of righting reflex and rotorod performance, and morphine-alcohol drug interaction were examined in the first 4 KO mice strains. These opioid and alcohol studies were conducted in this fashion in order to establish multiple converging lines of evidence of the crucial role of the innate immune system in drug response. In addition, molecular evidence was sought to support these behavioral data quantifying the activation of MAPK signaling ex vivo in WT and TLR4 KO mice.

Collectively, these data to be presented here highlight an important role that TLR signaling has in a broad range of opioid and alcohol actions individually and on their drug interactions between one another. Critically, these data highlight an as yet unexplored potential for intervention in alcohol and opioid misuse settings, and to improve the safety of clinically prescribed opioids. Development of therapeutics that target TLR activation by opioids and alcohol would be predicted to be valuable in the prevention/treatment of abuse of such drugs.

Learning Objectives:
- Role or proinflammatory immune signalling in alcohol response
- Role or proinflammatory immune signalling in opioid response
- An understanding of drug induced TLR signalling
- A basic understanding of pattern recognition receptors and their ligands

Literature References:
- Wu, Y et al. Inhibiting the TLR4/MyD88 signalling cascade by genetic or pharmacologic strategies reduces acute alcohol dose-induced sedation and motor impairment in mice. BJ Pharm. 2011; epub.
IMMUNE SIGNALING, NEUROIMMUNE GENE EXPRESSION AND REGULATION OF ALCOHOL CONSUMPTION

Robert Adron Harris PhD
University of Texas at Austin, Austin, TX

Genes classified as immune/stress response form one of the most prominent functional groups with differential expression in frontal cortex and VTA of alcoholics in comparison to nonalcoholics (Liu et al., 2006; Flatscher-Bader et al., 2006) and brain gene expression in mice that are genetically predisposed to alcohol consumption implicates pro-inflammatory mediators in brain may regulate alcohol intake (Mulligan et al., 2006). Based on these gene expression profiles, we selected six genes (β2m, cathepsin S (Cts), cathepsin F (Ctsf), interleukin 1 receptor antagonist (IL1ra), CD14 molecule (CD14, and interleukin 6 (Il6)) for behavioral validation using null mutant mice. Null mutant mice were tested for ethanol intake in three tests: 24 hr two-bottle choice, limited access two-bottle choice and limited access to one bottle of ethanol. Ethanol consumption and preference were reduced in all the null mutant mice in the 24 hr two-bottle choice test, the test that was the basis for selection of these genes. No major differences were observed in consumption of saccharin in the null mutant mice. Deletion of B2m, Cts, Il1ra, CD14 and Il6 also reduced ethanol consumption in the limited access two bottle choice test for ethanol intake; while the Il1ra and Cts null mutants showing reduced intake in all three tests (with some variation between males and females). We next asked if activation of the immune system could promote excessive alcohol consumption. We found that activation of inflammatory TR4 signaling (lipopolysaccharide, LPS, 1 mg/kg, i.p., C57Bl/6j mice) promotes alcohol consumption. This effect persisted at least 3 month after a single LPS treatment. No changes in taste (sweet or bitter) perception or palatability (sucrose intake) were found after LPS pre-treatment. The lack of CD14, a key component of TR4 signaling (CD14 knockout mice), as well a major proinflammatory cytokine – IL6 (IL6 knockout mice) prevented the increase of alcohol intake after treatment with LPS. These results support a novel role for neuroimmune signaling in regulation of alcohol consumption. Emerging results suggest that anti-inflammatory drugs can also reduce alcohol consumption and may be useful in treatment of alcohol abuse. Supported by the NIH/NIAAA (AA U01 13520 – NIA Project; and AA06399).

Learning Objectives:

- To understand brain gene expression changes in human alcoholics that are related to proinflammatory signaling.
- To understand genetic changes that reduce neuroinflammatory signaling in animal models and how they affect alcohol consumption.

Literature References:


Tuesday, May 29, 2012

PANEL
3:15 P.M. – 4:45 P.M.

ACTIVATION OF TR4 PATHWAYS BY OPiates AND COCAINE: IMPLICATIONS FOR ABUSE AND TREATMENT

Linda R. WatkinsI, PhD, Alexis Northcutt, Takato Hisanitou, PhD, Khara Ramos, PhD, Theresa Kopačić, PhD, Casey O’Neill, Florence Theberge, PhD, Yavin Shalaman, PhD, Steven F. Maijer, PhD, Ryan K. Bachtell, PhD, Jonathan L. Katz, PhD, Kenner C. Rice, PhD, Mark R. Hutchinson, PhD

IUniversity of Colorado-Boulder, Boulder, CO; Intramural Research Program, NIDA, Baltimore, MD, Intramural Research Programs of NIDA & NIAAA, Rockville, MD; University of Adelaide, Adelaide, South Australia, Australia

It has been known since the 1970s that opioids, cocaine and other stimulants can alter the function of glial cells and endothelial cells. However, it is only within the past 5 years that it has become clear that each drugs of abuse effect CNS neurons through a key anti-inflammatory receptor called toll-like receptor 4 (TLR4). This is in keeping with the recent recognition of TLR4 as an innate immune receptor whose functions include not only the recognition of pathogens and alarmins (signals of host cell stress and damage), but also the recognition of xenobiotics, that is, chemicals not expected to be present within an organism. The activation of TLR4 by such diverse chemical structures sets it apart from every neurotransmitter receptor classically studied in the drug abuse literature.

The study of the role of TLR4 in drug abuse arose as a natural extension of studies over the past 20 years documenting that glia (astrocytes and microglia) are activated under conditions of neurotrophic pain and that such glial activation powerfully contributes to such nerve injury-induced pain through the release of proinflammatory, neurotoxic substances. Notably, in 2004, it became clear that this pain-enhancing effect of glial activation was occurring, in part, through nerve damage induced release of alarmins, causing activation of TLR4. As, by then, glial activation had been implicated in the development of morphine tolerance, and many parallels exist in mechanisms underlying neuropathic pain and morphine tolerance, this link led us to initiate investigations of the role of TLR4 in various opioid effects. The results were striking. Blockade of TLR4 enhanced the utility of opioids for pain control; removing the opioid-induced, TLR4-mediated neuroinflammation increased the potency and duration of morphine analgesia while decreasing tolerance, dependence, opioid-induced constipation, and likely opioid-induced itch. In addition, we demonstrated that broadly inhibiting glial activation or specifically blocking TLR4 suppressed morphine-induced conditioned place preference (CPP) as well as morphine-induced dopamine elevations in the nucleus accumbens (NAC) shell. We have now documented parallel effects on cocaine-induced CPP and NAC-shell dopamine, in that both are suppressed by TLR4 blockade.

The study of the role of TLR4 in drug abuse was made possible through the discovery of (+)-naloxone and (+)-naltrxone as blood brain barrier permeable, selective TLR4 inhibitors. Characterization of these nociceptors, unusual isomers via radioisotopes and enzymatic assays of (-) and (R)-naloxone and (S) and (R)-naltrxone indicated that all four isomers are effective activators of TLR4. However, (+)-naloxone has a higher affinity for TLR4 than the other isomers and thus generates a greater signal as measured by reporter gene activity for either compound. Sigma-1 and sigma-2 receptor binding was also measured, as they have been hypothesized to underlie non-stereoispecific effects of opioids and effects of cocaine, with no effect of (+)-naloxone (or (+)-naltrxone) on dopamine, norepinephrine, or serotonin transporters. This selectivity, combined with their brain permeability, distinguishes (+)-naloxone and (+)-naltrxone from other TLR4 antagonists.

Studies currently underway are providing a broader examination of the role of TLR4 in the reinforcing effects of opioids and cocaine. Cell culture studies are exploring the effects of opioids and cocaine on TLR4-expressing CNS cells. In vivo (+)-naloxone and (+)-naltrxone have been found to suppress self-administration of opioid agonist, remifentanil, and cocaine. and, in pilot studies, to suppress cocaine reinstatement. Studies of heroin self-administration and incubation of craving are underway. Notably, barbituric for food in heroin-experienced rats is not suppressed by (+)-naltrxone, suggesting that performance deficits do not account for the suppression of self-administration. Taken together, the data suggest that targeting CNS TLR4 is a novel and promising approach for the treatment of drug abuse.

Learning Objectives:

- Learn about activation of glia and endothelial cells by opioids and cocaine
- Learn about the role of toll-like receptor4 in such glial activation
- Appreciate the effect that blocking toll like receptor 4 can have for responses of drugs of abuse
- Understand how (+)-naloxone and (+)-naltrxone may be new approaches for treating drug abuse

Literature References:

Tuesday, May 29, 2012

PANEL
3:15 P.M. - 4:45 P.M.

PANEL OVERVIEW:
RAPIDLY-ACTING ANTIDEPRESSANT THERAPIES: THE NIMH-SPONSORED
RAPID NETWORK

Maurizio Fava, MD, Carlos Zarate, MD, Mark Smith, MD, Michael Rohan, PhD

Massachusetts General Hospital, National Institute of Mental Health, \(^1\)Astra-Zeneca, \(^2\)McLean Hospital

None of the currently available pharmacologic and non-pharmacologic treatments for depression, as currently delivered, has been shown to result in rapid symptom resolution (defined as a sizeable and statistically significant treatment effect versus placebo that is apparent as early as 24 to 72 hours post-initiation of therapy), despite the fact that there is a tremendous need for rapid antidepressant therapies that would allow for meaningful clinical improvements. Over the last decade, a series of studies has demonstrated the ability of some novel approaches— including ketamine, an NMDA antagonist and sleep deprivation therapy— to provide significant amelioration of symptoms within a few hours, with symptoms typically returning within a period of days after discontinuation of the acute intervention. These promising results suggest that a more ambitious program of research might accelerate development of rapid-onset antidepressant treatments. Dr. Zarate will present the evidence for the rapid antidepressant effects of ketamine, whereas Dr. Paul will review the studies concerning the use of low field magnetic stimulation and its rapid effects on mood. Dr. Smith will present the rationale for developing non-ketamine, non-competitive NMDA-receptor antagonists in the treatment of depression, whereas Dr. Fava will introduce the design, methodological innovations, and implementation approaches adopted by the NIMH-sponsored RAPID Network, aimed at studying promising new treatments with putative rapid antidepressant effects.

Learning Objectives:
- To become more familiar with novel treatments aimed at improving depressive symptoms within 48 hours
- To understand putatively rapid antidepressant mechanisms of action

THE DESIGN AND IMPLEMENTATION OF THE RAPID NETWORK STUDIES

Maurizio Fava MD
Massachusetts General Hospital, Boston, MA

A number of design and methodological challenges face investigators who evaluate the efficacy of antidepressant treatments with putatively rapid effects. With respect to the design issues, expectations appear to play a major role in the very robust placebo responses that have been reported in the context of double-blind, single administrations of antidepressant therapies. Single-blind, placebo/sham lead-ins do not appear to be able to mitigate such effects, and parallel comparison designs carry very significant risks of high placebo response rates. Therefore, there is a clear need to adopt more innovative study designs to minimize such high placebo response risks. From a methodological standpoint, a major challenge is represented by the need to capture rapid changes in depressive symptoms. None of the most widely used clinician-rated and self-rated scales measuring depressive symptoms were developed with the intent of daily or hourly repeated uses. The typical timeframe for the use of scales such as the Hamilton Depression Rating Scale, the Montgomery-Asberg Depression Rating Scale, and the Inventory of Depressive Symptomatology is the week prior to the assessment. Again, there is a need to select modified versions of such scales and/or novel psychometric scales that are capable of detecting rapid changes in depressive symptoms. This presentation will review the background and rationale for the methodological and design approaches that were adopted in the NIMH-sponsored RAPID Network Studies. The presentation will also discuss some of the methodological innovations that have been planned in the implementation of these trials.

Learning Objectives:
- To become familiar with the methodological issues related to the conduct of studies assessing rapidly acting antidepressant treatments
- To learn the background and rationale of the methods adopted by the RAPID Network Studies

Literature References:
LOW FIELD MAGNETIC STIMULATION AND ITS RAPID EFFECTS ON MOOD

Michael Rohan¹, PhD, Steven M. Paul², MD
¹McLean Hospital, Belmont, MA; ²Weill Cornell Medical College, New York, NY

Low Field Magnetic Stimulation (LFMS) is a novel rapidly alternating magnetic field that noninvasively induces an electric field in brain and which has recently been shown by Rohan and colleagues to have a rapid antidepressant effect within 20 minutes in both bipolar and unipolar depressed patients. More recently several laboratories have demonstrated that LFMS has antidepressant effects in the Forced Swim Test (FST), a commonly used animal model for detecting active antidepressant agents. LFMS had similar antidepressant effects in the FST to those observed with both SSRIs and SNRIs. Volkow and colleagues have also recently studied the effects of LFMS on brain metabolism in healthy volunteers using FDG-PET and have demonstrated reductions in brain glucose utilization (brain metabolism) that are directly proportional and regionally localized to the LFMS-induced electric fields in brain. Although the precise neurophysiological basis for these changes in brain metabolism is unknown several plausible mechanisms exist whereby relatively low energy electric fields induced by LFMS have been shown to polarize neurons and to alter their endogenous electrical activity as well as local neural circuits. Taken together, LFMS appears to rapidly elevate mood in depressed patients and thus may represent a safe and rapid intervention for treating depression upon repeated administration. The literature on LFMS will be critically reviewed and a development framework for testing LFMS as a potential rapid treatment for depression will be outlined.

Learning Objectives:
- To become familiar with LFMS as a potential rapid treatment for depression
- To understand how LFMS might work and why it is different from other neuromodulation approaches for treating depression.

Literature References:

KETAMINE AS A RAPIDLY ACTING ANTIDEPRESSANT

Carlos Zarate, MD
National Institute of Mental Health, Bethesda, MD

Introduction: Accelerating the antidepressant effects from weeks to hours or days is now a major goal of depression treatment research. Achieving this goal would likely result in a significant reduction in morbidity and mortality associated with depression. Pharmacological strategies that rapidly reverse depressive symptoms including suicidal ideation would have an enormous impact on public health. Several converging lines of evidence suggest that dysfunction of the glutamatergic system—particularly the N-methyl-D-aspartate (NMDA) and AMPA receptors and their respective subunits—may play important roles in the pathophysiology of major depressive disorder (MDD) and bipolar depression (BDP). Therefore, testing the efficacy of glutamatergic modulators could yield an improved knowledge of the neurobiological processes involved in these complex illnesses, and lead to the development of radically improved treatments.

Methods: Six controlled trials with NMDA antagonists have been conducted to date at NIMH in major depression (1 double-blind placebo-controlled study with memantine, and 4 controlled studies with the NMDA antagonist ketamine, and 1 with the NR2B antagonist MK-0657). In addition, we have obtained biomarker data using electrophysiological recordings (polysomnography [PSG], magnetoencephalography [MEG]), neuroimaging (positron emission tomography [PET], magnetic resonance spectroscopy [MRS]) as neural correlates of antidepressant response to ketamine.

Results: In all controlled studies with ketamine, a rapid antidepressant response was found. In the first study in MDD, we found an onset of antidepressant action within 110 minutes. The effect size for the drug difference was very large (d=1.46) after 24 hours and large (d=0.68) after 1 week. In the BPD study, we found an antidepressant response within 40 minutes (d=0.52); this improvement remained significant through Day 3. A recent study, which will be presented for the first time, was completed in BPD which also showed rapid antidepressant response within 40 minutes lasting 3 days. In addition, in this study we found that ketamine in this controlled study resulted in rapid antisucidal effects. Finally, we will present for the first time, the results of the NR2B antagonist MK-0657 in treatment-resistant depression. With regards to biomarkers predicting antidepressant response, we found that pregenual anterior cingulate cortical activity in response to an emotional and cognitive task predicted antidepressant improvement to ketamine and gamma power cortical activity correlated with decreases in depressive symptoms following ketamine infusion.

Conclusions: Modulating the glutamatergic system particularly at the NMDA receptor complex appears to be important to the mechanism of immediate antidepressant response. Electrophysiological and neuroimaging studies are yielding important insights into the neural correlates of rapid antidepressant action.

Learning Objectives:
- The participant will learn about the importance of the glutamate system in depression.
- The participant will understand studies being conducted with NMDA modulators in depression.
- The participant will understand studies to develop rapid acting antidepressants.

Literature References:
- Zarate et al. Arch Gen Psychiat 2006; Diazgranados et al. 2010.
THE ROLE OF NON-KETAMINE, NON-COMPETITIVE NMDA-RECEPTOR ANTAGONISTS IN THE TREATMENT OF DEPRESSION

Mark A. Smith, MD, Carla Maciag, BS, Michael Quirk, PhD, Sanjeev Pathak, MD, Timothy Piser, PhD, Dennis McCarthy, PhD, Robert Alexander, MD, Gerard Sanacora, MD

1AstraZeneca, Wilmington, DE, 2Yale University, New Haven, CT

While evidence for a rapid (<24 hr) antidepressant effect of the dissociative anesthetic ketamine continues to accumulate (1,2), it remains to be seen whether other NMDA antagonists that have an improved tolerability profile will also prove efficacious. Low affinity, low trapping NMDA antagonists such as memantine and remacimide, as well as NR2B-selective compounds like MK-0657, appear to avoid the psychotomimetic effects and cognitive impairment induced by ketamine. The question is whether such compounds will prove to have rapidly occurring, mood-elevating properties. So far only the NR2B-selective NMDA antagonist (CP-101,606) has been reported to have antidepressant effects (as an adjunct agent) with a time course that was on the order of days rather than hours (3). Here we describe recent findings pertaining to the testing and translation of potential non-competitive NMDA receptor antagonists into humans that may be useful in treating depression and anxiety. In order to identify such drugs, we tested a variety of compounds in a novel rat prenatal stress model that assesses aspects of non-appetitive motivation. Pregnant dams were stressed during the third week of gestation, and then the offspring were tested for exploratory activity as young adults in the elevated plus maze. Prenatally stressed rats were sensitive to noradrenergic and dopaminergic antidepressant mechanisms, but interestingly insensitive to serotonergic reuptake blockers. Several novel drug classes effectively increased the motivation to explore. Ketamine as well as CP-101,606 produced long-lasting effects in this model after a single administration which parallel their reported antidepressant effects. Memantine, which has relatively low trapping within the closed channel of the NMDA receptor, was also active in the rat model, but initial clinical trials in depression have been negative (4). This could reflect problems with translating preclinical results to man, or it could reflect technical problems trying to detect rapid antidepressant effects within 48 hr. For example, our experience suggests that there is a large expectancy of a positive response to a putative fast-acting antidepressant even in patients with a history of inadequate response to standard antidepressants which exacerbates the problem of placebo response. Clearly there is a need for improved protocol designs as well as the validation of new scales and endpoints suited to the detection of rapid mood effects. This will facilitate the testing of novel, non-ketamine, NMDA antagonists and other glutamatergic targets in short-term trials in depressed patients.

Learning Objectives:
- Learn about efforts to develop non-ketamine NMDA antagonists with improved risk/benefit ratios for treating depression
- Learn about challenges in demonstrating rapid antidepressant effects in the clinic

Literature References:
NIMH UPDATE
Phillip S. Wang, MD
National Institute of Mental Health, Bethesda, MD

Although the enormous burdens from mental illness continue, pharmaceutical and biotech companies have been deterred from investing in CNS drug development due in part to some costly late-stage failures. Reversing these trends will require identifying new therapeutic targets and derisking them. This presentation will provide an overview of some recent research findings illustrating potential disease mechanisms and new therapeutic targets. Findings such as these may offer translational opportunities to develop the next generation of treatments for mental illness.

COMMON TARGETS ACROSS BRAIN DISEASES: NEW OPPORTUNITIES TO TREAT SUBSTANCE USE DISORDERS (SUDS)
Phil Skolnick, PhD
NIH, NIDA, Bethesda, MD

Currently, there are no medications approved to treat either stimulant (e.g., cocaine, methamphetamine) or cannabis dependence, and approved pharmacotherapies to treat other SUDs (e.g., opiates, tobacco) are far from ideal. For example, no more than 20% of smokers are able to sustain "long term" (12 month) abstinence, despite the availability of therapeutic options to treat tobacco dependence (nicotine replacement therapies, bupropion, and varenicline). The pharmaceutical industry has largely neglected the development of medications to treat SUDs. The result of this indifference is that significant therapeutic advances are most likely to emerge from an understanding of the neurobiological processes common to SUDs and other neuropsychiatric disorders. Successful translation of this knowledge relies predominantly on the use of repurposed molecules. Based on this principle, I will describe molecules currently in either mid or late-stage clinical development that may represent new pharmacotherapies to treat SUDs.
MEDICATIONS DEVELOPMENT FOR ALCOHOL DEPENDENCE: A VISION FOR THE NEXT DECADE

Kenneth R. Warren, PhD
National Institute on Alcohol Abuse and Alcoholism, Rockville, MD

Alcohol Use Disorders (alcohol abuse and dependence) are among the most prevalent mental health disorders found in the world today. More than 76 million people worldwide are estimated to have diagnosable alcohol use disorders. Pharmacotherapy offers promising means for treating alcohol dependence, and significant progress has been made in the past 20 years. Currently, four medications have been approved by the U.S. Food and Drug Administration for alcoholism, the last three within the past two decades. Unfortunately, these medications do not work for everyone; as a result, active research continues to search for effective medications to treat an even wider range of patients. National Institute on Alcohol Abuse and Alcoholism (NIAAA) is committed to the vision of ensuring the development and delivery of new and more effective alcohol medications over the coming decade. To facilitate this, the NIAAA has identified 7 key objectives: 1) to discover and validate new molecular targets for the treatment of AUDs. This effort holds the promise of identifying novel therapeutics as well as more favorable side effect profiles; 2) to develop and implement animal and human laboratory paradigms as screening models for drug development; 3) to bridge the often-discussed gaps in the drug development process (referred to as the “Valley of Death”) through a fully translational therapeutics development program; 4) to develop methodological approaches for conducting AUD clinical trials that are more efficient, both in terms of their economic and time costs; 5) to advance personalized medicine in the pursuit of new compounds, as a means of increasing the effect size in adequately selected patients; 6) to identify and remove barriers to the implementation and adoption of alcohol medications in real-world treatment settings; and 7) to facilitate the development of collaborative networks and partnerships among pertinent stakeholders seeking new therapeutics for addictive disorders, such as the Federal government, the pharmaceutical industry, academia, healthcare organizations, as well as patient and advocacy groups. Successful implementation of these objectives will result in the development of more efficacious and safe medications, provide a greater selection of therapy options, and ultimately lessen the impact of this devastating disorder.

TRANSLATIONAL THERAPEUTICS DEVELOPMENT AT NIH

Christopher P. Austin, MD
National Center for Advancing Translational Science, Bethesda, MD

The explosion in mechanistic understanding of human physiology in health and disease, exemplified by the Human Genome Project and its successors, has provided a deluge of potential new targets for therapeutic development. At the same time, evolution of technologies and operational systems for drug discovery has allowed investigators and institutions in the public sector to contribute directly to new therapeutics discovery in a more vigorous way, particularly for rare and neglected diseases. Over the last decade, the NIH has built a variety of programs which complement drug discovery efforts in the biopharmaceutical sector, principally in two areas: (a) science, technology, tool, and paradigm development to improve scientific understanding and efficiency of the therapeutics discovery process, and (b) early stage drug development programs to de-risk projects particularly for rare and neglected diseases, making them more amenable to biopharmaceutical adoption despite their low expected return on investment. The mission and accomplishments of these programs will be discussed.
PANEL OVERVIEW:
NEUROENDOCRINE CHANGES IN MDD AND BD: CLINICAL AND BIOLOGICAL MARKERS

Dorothy S. Ts' MD, David Kemp', MD, Barbara Parry', MD, Wendy Marsh', MD, Claudio Soares', MD

1University of Pittsburgh, Western Psychiatric Institute and Clinic, 2Case Western Reserve University, 3University of California, San Diego, 4University of Massachusetts Medical School 5McMaster University

Medical disease, circadian disruption and hormone-responsive life cycle events are associated with increased symptoms, chronicity and disability in Bipolar Disorder (BD) and Major Depressive Disorder (MDD). This symposium features cutting-edge research on neuroendocrine clinical and biomarkers (glucose metabolism, circadian rhythms, pregnancy, postpartum and menopause) which will extend knowledge of the phenomenology of mood disorders, relationships between psychiatric and medical conditions and future directions in treatment development. An innovative model for developing new treatment involves the study of insulin sensitizing drugs (e.g. pioglitazone) as potential mood modulators. Speaker 1 discusses how data on biological mediators of insulin resistance and depressive symptoms support exciting preliminary evidence of the novel antidepressant effects of pioglitazone. Speaker 2 (Chair) discusses the effects of gestational diabetes and maternal mood disorders on adverse infant outcomes (preterm birth, birth weight and peripartum events). Discussion will focus on the intriguing findings that glucose metabolism was not associated with adverse outcomes whereas maternal diagnosis was associated with increased perinatal events. Speaker 3 discusses her elegant longitudinal research on circadian rhythms in melatonin, sleep, cortisol, prolactin and TSH release in women with depressive disorders and circadian factors which predict menopausal depression risk. Focussing on the menopausal transition, Speaker 4 addresses risk of mood episodes, hot flashes and reproductive hormones in perimenopause. Note: the session proposal includes presenters who are past recipients of the NCDEU New Investigator Award.

Learning Objectives:
- Identify comorbid medical/psychiatric conditions related to BD/MDD.
- Describe neuroendocrine clinical and bio-markers related to BD/MDD.
- Develop management plans which involve screening and treatment of comorbidities.

INSULIN SENSITIZERS AS MODULATORS OF MOOD: RATIONALE AND PRELIMINARY EVIDENCE FOR THE USE OF PIOGLITAZONE IN THE TREATMENT OF MAJOR DEPRESSIVE EPISODES

David Kemp, MD
Case Western Reserve University, Cleveland, OH

Insulin resistance and other cardiometabolic conditions disproportionately affect patients with mood disorders, lead to poorer treatment outcomes, and increase the risk of premature death. Reflective of overlapping pathophysiology, many of the physiologic systems implicated in the development of insulin resistance also regulate mood and behavior, including inflammatory networks, neuroendocrine stress markers, and sympathetic nervous system activation. In animal models, the insulin sensitizer, pioglitazone, has been shown to mitigate damage from inflammatory insults, induce neuroprotection, and demonstrate antidepressant-like effects. To explore its antidepressant effects in humans, we conducted a proof-of-concept, open-label study of pioglitazone administration in 70 patients experiencing major depressive episodes. Pioglitazone was associated with significant improvement in depression severity as measured by baseline-to-endpoint reduction on the Inventory of Depressive Symptoms (IDS) total score among unipolar (19.1 ± 1.9; p<0.01) and bipolar (14.2 ± 2.1; p<0.01) depressed patients. Pioglitazone improved insulin sensitivity and was associated with a reduction in Interleukin-6 (IL-6), highly-sensitive C-reactive protein and atherogenic dyslipidemia. Among unipolar depressed patients, change in IL-6 was correlated with improvement in IDS scores(p=0.06). Inferential analysis suggested a greater therapeutic effect size (Cohen's d) on IDS change scores among patients in the upper tertile of IL-6 (26.2 vs. -17.7; d=0.78) at baseline. In contrast to conventional treatments that can worsen insulin resistance and dyslipidemia, pioglitazone may represent a novel modulator of mood that acts by increasing insulin sensitivity and decreasing inflammation.

Learning Objectives:
- Describe the pathophysiologic mediators of insulin resistance and their potential influence on the development and course of depressive symptoms.
- Review the preliminary evidence in support of pioglitazone as a novel intervention to reduce depression severity and improve markers of cardiometabolic health.

Literature References:
GESTATIONAL DIABETES AND OBESITY IN PREGNANT WOMEN WITH MAJOR DEPRESSIVE DISORDER OR BIPOLAR DISORDER VS HEALTHY CONTROLS: EFFECTS ON ADVERSE NEONATAL OUTCOMES (PRETERM BIRTH, BIRTH WEIGHT AND PERIPARTUM EVENTS)

Dorothy Sit, MD
University of Pittsburgh, Western Psychiatric Institute and Clinic, Pittsburgh, PA

**Background:** Gestational diabetes (GDM) affects 7% of pregnant mothers. Pre-pregnancy BMI and obesity are linked with GDM plus increased odds for mood disorders. GDM and maternal obesity contribute to adverse outcomes - pregnancy loss, pre-eclampsia, surgical delivery, eventual DM and newborn complications. We explored the relationship of GDM and maternal mood disorders with adverse outcomes.

**Methods:** We examined Healthy Control mothers (HC), mothers with Major Depressive Disorder (MDD) and Bipolar Disorder (BD) during pregnancy and at delivery to record pre-pregnancy BMI and confirm diagnosis with the SCID interview. At 28wks gestation, mothers received the 1-hr 50g oral glucose challenge test (GCT). Outcome variables were preterm birth, birth weight and peripartum events.

**Results:** We enrolled 48 HC, 15 BD, 42 past MDD and 32 current MDD mothers. Mothers with BD differed significantly from the others with lower rates of completing college and being married, plus increased substance use. Pre-pregnancy BMI, mean GCT and the rate of impaired glucose metabolism (GCT > 140mg/dL) did not differ significantly across groups. Glucose metabolism was not associated with perinatal events, birth weight or preterm birth. Maternal diagnosis was associated with increased perinatal events.

**Conclusion:** Genetic-environmental factors e.g. health behaviours, medication effects, abnormal stress response or familial risk may contribute to adverse obstetrical outcomes in mothers with mood disorders.

**Key Words:** Diabetes, Obesity, Depression, Bipolar Disorder, Adverse Outcomes.

**Learning Objectives:**
- Understand the risk and how to identify for gestational diabetes, obesity or weight gain problems in pregnant and postpartum mothers with BD or MDD in a general psychiatric clinic.
- Be aware to discuss with patients about risks/benefits of medication treatments for BD or MDD which may contribute to GDM, obesity or excessive/insufficient wt gain in pregnancy.
- Incorporate proper monitoring for comorbid disorders e.g. diabetes, wt gain and metabolic problems in women with BD or MDD.
- Be able to enlist other providers e.g. obstetrician, pediatrician and primary care physician in providing patient focused team approach to care for the mother-infant pair.

**Literature References:**

CIRCADIAN AND HORMONAL CHARACTERISTICS OF MENOPAUSAL WOMEN WITH MAJOR DEPRESSION VS NORMAL CONTROLS

Barbara L. Parry, MD
University of California, San Diego, La Jolla, CA

**Aim:** We hypothesized that the amplitude or phase (timing) of melatonin and other circadian rhythms differs in menopausal depressed patients (DP) vs. normal control (NC) women.

**Methods:** In 38 (24 NC, 14 DP) peri- or post-menopausal women, we measured plasma melatonin and serum cortisol, TSH and prolactin every 30 minutes from 18:00-10:00 h in dim light (< 30 lux) or dark, serum gonadotropins and steroids (18:00, 06:00 h), mood (Hamilton and Beck depression ratings) and subjective (logs) and objective (polysomnography-PSG) sleep.

**Results:** Multi- and univariate analyses of covariance (MANCOVA, ANCOVA) showed melatonin offset time was delayed (P = .045) and morning plasma melatonin was elevated in DP compared with NC (P = .044). Multiple regression analyses showed that years past menopause predicted melatonin duration, and that melatonin duration, body mass index (BMI), years past menopause, Follicle Stimulating Hormone (FSH) level and sleep end time were significant predictors of baseline Hamilton P (P = .0003) and Beck (P = .00004) depression scores. Cosinor acrophase, amplitude, mesor for cortisol, TSH and prolactin were not significantly different in DP vs. NC. Sleep logs, but not PSG, showed poorer sleep quality in DP vs. NC.

**Conclusions:** Increased melatonin secretion that is phase-delayed into the morning characterized menopausal DP vs. NC. Years past menopause, FSH, sleep end time and BMI may modulate effects of altered melatonin secretion in menopausal depression. Cortisol, TSH and prolactin circadian rhythms were not significantly different in DP vs. NC. DP had poorer sleep quality by subjective, but not objective, assessments.

**Learning Objectives:**
- Understand the circadian rhythm disturbances in menopausal depression
- Understand the clinical factors that predict menopausal depression

**Literature References:**
THE MENOPAUSAL TRANSITION: RISK OF MOOD EPISODES AND THE CLINICAL BIOMARKER OF REPRODUCTIVE HORMONES

Wendy Marsh1, MD, Sybil Crawford2, PhD, Joyce Bromberger3, PhD, Claudio Soares4, MD

1University of Massachusetts Medical School, Worcester, MA; 2University of Massachusetts, Worcester, MA; 3University of Pittsburgh, Pittsburgh, PA; 4McMaster University, Hamilton, Ontario, Canada

Introduction: Multiple longitudinal studies now report the menopausal transition as a time of increased risk of depression in women with or without a history of depression. During the menopausal transition the estradiol levels or variability thereof have been assessed in association with depression symptoms, here we look at estradiol history during the reproductive years and risk of depression during the menopausal transition.

Methods: The community based, 7-site Study of Women's Health Across the Nation (SWAN) provided data on reproductive history at entry and menopause-related and depression symptoms annually for ten years. The association of estradiol exposure variables in the reproductive years with time to first visit depressed (Center for Epidemiologic Studies Depression (CES-D) ≥16) after premenopause, i.e. peri or postmenopausal was estimated using pooled logistic regression.

Results: Estrogen exposure variables during the reproductive years are associated with risk of depression during the menopausal transition. The duration of estradiol exposure or later age of onset of perimenopause was found to be protective against depression during the menopausal transition.

Conclusion: Risk of depression during the menopausal transition is complex and associated with reproductive endocrinology not just current but historic as well.

Learning Objectives:
- The menopausal transition is a time of increased risk of depression.
- Depression risk during the menopausal transition has been assessed related to concurrent hormonal changes,
- Depression risk during the menopausal transition is also associated with a woman's reproductive hormonal history

Literature References:
- Freeman E. Association of depression with the transition to menopause. Menopause 2010; 17:823-27.
CURRENT ANTIDEPRESSANT MEDICATIONS ARE EQUALLY EFFECTIVE IN GENERAL POPULATIONS OF MAJOR DEPRESSION. HOWEVER, ONLY A MINORITY OF PATIENTS ACHIEVE SYMPTOMATIC REMISSION WITH ACUTE MONOTHERAPY WITH ANY ANTIDEPRESSANT. SUSTAINED FUNCTIONAL BENEFIT WITH ACCEPTABLE TOLERABILITY REMAINS AN ENDURING CHALLENGE. IN SPITE OF THE PUBLIC HEALTH IMPACT OF SUICIDE, NO TREATMENT HAS PROVEN REDUCED MORBIDITY OR MORTALITY FROM SUICIDAL BEHAVIOR IN MAJOR DEPRESSION. THE LACK OF GENOMIC MARKERS IN PSYCHOPATHOLOGY IS A DISADVANTAGE IN PERSONALIZING PSYCHOTROPICS. IS THE FAILURE OF TRADITIONALLY NOVEL ANTIDEPRESSANTS ACHIEVING REGULATORY APPROVAL OVER THE PAST 2 DECADES DUE TO ASSET LIMITATIONS OR DEFICIENT PROGRESSIVE MENTAL IN DEVELOPMENT? SHOULD THE OPPORTUNITY FOR SERENDIPITOUS DISCOVERY BE REVISITED?

ADVANCES IN NEUROSCIENCE OPEN NOVEL SYMPTOMATIC AS WELL AS POTENTIAL DISEASE MODIFICATION APPROACHES IN MAJOR DEPRESSION. TAKING ADVANTAGE OF NOVEL ASSET REQUIREMENTS IMPROVES PRECISION OF OUTCOME MEASURES, AS WELL AS ADVANCES IN BIOMARKER/BIOLOGICAL SCALES. CURRENT RATING SCALES ARE LARGELY BASED ON OBJECTIVE DATA AND DO NOT REFLECT KNOWLEDGE IN THE NEUROSCIENCE. THE UNIQUE PHARMACOLOGICAL STRENGTHS OF A DRUG IN DEVELOPMENT CANNOT BE LEVERAGED IN CLINICAL TRIALS DUE TO THE LIMITATIONS CURRENT CLINICAL TRIAL METHODOLOGIES, INCLUDING OBSOLETE RATING SCALES.

SUCCESSFUL REGULATORY PATHWAYS INCLUDE A GLOBAL LABEL FOR MAJOR DEPRESSION, AUGMENTATION OF MONOTHERAPY AND TREATMENT RESISTANT DEPRESSION. ADDITIONALLY, SYMPTOMATIC INDICATIONS (E.G. IRRITABILITY, AGGRESSION) EXIST FOR OTHER PSYCHOTROPICS. SEVERAL DELINEATED REGULATORY PATHWAYS PROVIDE GUIDANCE FOR DECISIONS IN DRUG DEVELOPMENT.

MAJOR DEPRESSION COMPETES WITHIN NEUROSCIENCE AS WELL AGAINST OTHER THERAPEUTIC AREAS FOR FINITE RESOURCES. THE PROBABILITY OF TECHNICAL AND REGULATORY SUCCESS INFLUENCES CHOICES IN INVESTMENT. AN ADDITIONAL REALITY IS THE POTENTIAL RETURN ON INVESTMENT DURING THE PERIOD OF EXCLUSIVITY BOTH IN DEVELOPED COUNTRIES AND GLOBALLY. EXECUTIVE DECISIONS INCORPORATE THE REALITY OF PAYER VARIABLES IN DECISION MAKING AMONG THERAPEUTIC AREA CHOICES.

LEARNING OBJECTIVES:
- Describe the expected benefits from tomorrow's antidepressants
- Learn neuroscience driven improvements in measurement of depression
- Discuss symptoms and subpopulation targets in major depression
- Describe how depression competes with other therapeutic areas in drug development

TARGETS FOR PHARMACOLOGICAL INTERVENTION IN MDD

DOUGLAS E. FELTNER MD
DOUGLAS E. FELTNER, LLC, NOVI, MI

DISCOVERING NEW PHARMACOTHERAPIES FOR MAJOR DEPRESSIVE DISORDER (MDD), AND PROVIDING THE FIRST EVIDENCE OF HUMAN EFFICACY FOR THEM, IS A MAJOR CHALLENGE. NEW APPROACHES ARE NEEDED. AFTER BRIEFLY REVIEWING THE STRENGTHS AND LIMITATIONS OF COMMONLY EMPLOYED CURRENT PHARMACOLOGICAL METHODS USED IN THE DISCOVERY OF ANTIDEPRESSANTS, A TRANSLATIONAL MODEL TO ADDRESS SOME OF THE CHALLENGES IN DISCOVERING AND DEVELOPING NEW MDD PHARMACOTHERAPIES WILL BE PRESENTED. ELEMENTS OF THIS MODEL INCLUDE IDENTIFICATION OF THE FINAL COMMON PATHWAY OF MDD AS A DEFICIT IN REWARD SEEKING AND/REWARD EXPERIENCE, IDENTIFYING DEFICITS IN HUMAN NEURAL CIRCUITRY AS A KEY TRANSLATIONAL TARGET FOR DEMONSTRATING PHARMACODYNAMIC ACTIVITY, LINKING TARGET MODULATION TO HUMAN DISEASE PATHOPHYSIOLOGY, USING PATIENT STRATIFICATION TO CREATE A MORE PATHOPHYSIOLOGICALLY HOMOGENEOUS STUDY POPULATION, AND TRANSLATIONAL DEMONSTRATION OF EXTENT AND TYPE OF TARGET MODULATION. CANDIDATE METHODS FOR STRATIFICATION, INCLUDING BIOMARKERS, GENETICS, STRUCTURAL MRI AND FUNCTIONAL MRI WILL BE ILLUSTRATED WITH POTENTIAL EXAMPLE INDICATIONS. AN ATTEMPT WILL BE MADE TO EXTEND THE MODEL TO DISCERN ITS USEFULNESS FOR IDENTIFYING ANTIDEPRESSANTS WITH GREATER EFFICACY THAN CURRENT TREATMENTS, AND ANTIDEPRESSANTS THAT MAY PREVENT NEUROPATHOLOGIC PROGRESSION OF MDD. METHODOLOGIC LIMITATIONS WILL BE IDENTIFIED AND SUGGESTIONS WILL BE MADE FOR OVERCOMING THEM.

LEARNING OBJECTIVES:
- Participants will learn about challenges in antidepressant discovery and early development
- Participants will learn about new translational approaches for antidepressants
- Participants will learn about patient stratification approaches to antidepressant development

LITERATURE REFERENCES:
PRECISION IN OUTCOME MEASURES

Philip T. Ninan, MD
Pfizer, Collegeville, PA

Rating scales permit grading of symptoms, functioning and global observations. They serve as outcome measures in clinical trials and are the basis of regulatory claims. Diagnostic criteria categorize individuals with a disorder. Rating scale scores can provide proxies for diagnostic thresholds from which economic indicators can be imputed. In the absence of validated biomarkers in Major Depressive Disorder (MDD), outcome measures based on subjective report become critical observations.

The development of a new patient reported outcome scale to measure depression, its item generation and content validation, is described. It follows the path set forth in a recent FDA guidance, and incorporates symptoms with measures of quality of life and function (in social, work, school, home and in personal grooming/hygiene). Subsumed in the scale is the ability to examine the relationship of depressive symptom severity and disability, diagnostic thresholds for MDD and GAD, change scores with treatment, including the clinical relevance of the change.

The new scale incorporates knowledge in the neurosciences, distinguishing emotions, cognition and behavior, and their interrelations. Emotional anxiety is coupled with its associated cognition of worry and the behaviors of agitation and avoidance. Sadness is coupled with sad and suicidal cognitions, and behavioral withdrawal. Lack of positive emotions or anhedonia, is connected to scarcity of thought, lack of interest and physical fatigue. Additionally, social cognition is measured as lack of compassion and distrust of others. Other items assess the process of mentation (attention, memory), neurovegetative symptoms (appetite, sleep), somatic sense of well-being and stress reactivity (distress).

Improving the precision of measurement of depression may enhance signal detection in placebo controlled studies, as well as potential superiority of one treatment over another.

Learning Objectives:
- Discuss the shortcomings of current depression scales
- Examine the process and content of developing a new rating scale

Literature References:

PATHWAYS TO REGULATORY APPROVAL IN MDD

Brendon Binneman MD
Pfizer, Groton, CT

There are multiple pathways for approval of a new medication for MDD. Monotherapy for unselected MDD has been the most common historical approach and has resulted in TCAs, MAOIs, SSRIs, SNRIs and a few others not falling cleanly into the above classes. These medicines in these classes are considered broadly equivalent, though occasional studies and clinical practice implies some advantage in specific subpopulations. Thus acute treatment with current antidepressants achieve response in the majority of subjects, and remission in a minority. There is typically a delay in the onset of benefits counted more in weeks than days. Sustained response over a one year period occurs in the majority of individuals. No treatment has a claim for efficacy in suicidal behavior in MDD.

A fixed dose combination of fluoxetine and olanzapine is the only approved medication for treatment resistant depression. Two second generation antipsychotic (SGA) drugs have received approval as adjunctive treatment of MDD. Both are for short term use only, with no claim for maintenance efficacy. Quetiapine has a claim for efficacy in bipolar depression. Additionally, efficacy claim for symptom benefits (analogous to irritability associated with autistic disorder and agitation associated with schizophrenia) in MDD is a potential regulatory pathway.

Generic versions of most branded antidepressants are available currently or will be shortly. Return on investment models are unlikely to support development of a new antidepressant medication that demonstrates similar efficacy to current generics. Superiority is a challenging goal given the poor signal detection capabilities of outcome scales and clinical trial process. A possible approach is to aim for superiority in MDD subpopulations with supportive biomarkers. These potential subpopulations include MDD associated with stress sensitization in individuals with a history of trauma or early life abuse, MDD associated with cytokine activation (e.g. inflammatory diseases such as rheumatoid arthritis), and MDD presenting for the first time in the elderly where vascular features have a suggested role. Additionally, potential symptom targets in MDD include apathy, impulsivity, and suicidal behavior.

Learning Objectives:
- Summarize precedent pathways to regulatory pathways in MDD
- Summarize potential future directions in MDD drug development
COMPETING DRIVERS INFLUENCING EXECUTIVE DECISIONS

Steve Romano, MD
Pfizer, New York, NY

Given the unmet need in the treatment of Major Depressive Disorder (MDD) and the dramatic advances in neuroscience knowledge, the developmental failure of truly novel antidepressant treatments is problematic. For novel antidepressant development, challenges include moving from disorder to disease models, lack of validated biomarkers, obstacles in precision medicine and subjective endpoints. Economic, including the need to focus limited research dollars on areas where risk can be sequentially and confidently reduced to support next-stage funding, as well as other factors have prompted the exit of prominent pharmaceutical companies from MDD development. In comparison with several other therapeutic areas, psychiatry and neurology product development takes longer and is riskier, with lower probability of technical and regulatory success. Health technology assessments and the demands of payers who value only those new treatments with relevant differentiation from standard of care is an additional hurdle. The hope that small biotechnology firms with venture capital resources can step into the development vacuum is overly optimistic, given the short horizon of such funding. The investment shortfall in depression treatment development contrasts with the high personal and societal costs of inadequately treated disease. As with other disease areas where rational drug discovery and development has been enabled by enhanced understanding of the underlying biology and more relevant translational models, basic research elucidating underlying pathophysiology of key disease dimensions may be necessary to reclaim more scarce research and development dollars.

Learning Objectives:
- Discuss the unmet needs in the treatment of MDD
- Describe the factors influencing antidepressant drug development

Literature References:
NEUROCHEMICAL ALTERATIONS IN ADOLESCENT MARIJUANA ABUSERS

Andrew P. Prescot, PhD, Perry F. Pena, MD, Deborah E. Yurgelun-Todd, PhD

Brain Institute, University of Utah, Salt Lake City, UT

Background: Converging evidence from neuroimaging and neuropsychological investigations suggest that prefrontal cortical functional and structural alterations are detectable in both adult (1) and adolescent chronic marijuana users compared to non-using controls (2-3). Our proton (1H) magnetic resonance spectroscopy (MRS) studies have demonstrated reduced anterior cingulate cortex (ACC) Glu levels detected in adolescent chronic marijuana smokers compared to non-using controls (4). Exogenous cannabinoids are known to exert similar effects on presynaptic glutamate and γ-amino butyric acid (GABA) release, and we hypothesized that lower ACC Glu levels detected in adolescent chronic marijuana smokers will be paralleled by comparable reductions in ACC GABA levels. The present study applied metabolite-editing 1H MRS techniques to measure changes in ACC GABA levels in adolescent marijuana users compared to non-using controls.

Methods: Adolescent marijuana (MJ) users (N = 13; average age 18 ± 1 years) and similarly aged healthy control (HC) subjects (N = 16; average age 16 ± 2 years) were enrolled and scanned using a Siemens 3T Trio MRI system. Clinical variables recorded from all MJ subjects included age of first use, age of regular use, and total marijuana use. Conventional and GABA-editing (MEGAPRESS) 1H MRS methods were used to acquire MRS data from a 22.5 mL voxel positioned bilaterally within the ACC. MEGAPRESS spectra were fitted using automated MATLAB routines, and GABA levels were normalized to a scaled unsuppressed water PRESS signal integral corrected for CSF fraction. Group mean metabolite levels were statistically evaluated using two-tailed t-tests.

Results: GABA levels were significantly lower in the MJ cohort (MJ 0.63 ± 0.12; HC 0.81 ± 0.25) and, in agreement with our previous study, the MJ subjects showed significantly lower ACC Glu (MJ 4.84 ± 0.52; HC 5.61 ± 0.88) levels. Statistical significance remained for both GABA and Glu after co-varying for subject age. Correlation analysis showed a trend towards a significant negative relationship between GABA levels and total MJ use (r = -0.54, p = 0.06).

Conclusions: These data infer that altered glutamatergic and GABAergic status is associated with chronic marijuana exposure during adolescence, adding to the neuroimaging data reporting altered cingulate function in individuals with marijuana-abuse. The development of future clinical and preclinical protocols pertinent to adolescent marijuana exposure will be discussed.

Learning Objectives:
- Neuroimaging and neurochemical alterations in adolescent chronic marijuana users
- MRS methods for GABA detection
- Preclinical animal models of adolescent chronic cannabinoid exposure

Literature References:
GABAergic AND DOPAMINERGIC CHANGES IN SCHIZOPHRENIA

Lawrence S. Kegeles, MD
Columbia University, New York, NY

Background: Postmortem studies have found evidence of GABA deficits in fast-spiking, parvalbumin-positive interneurons in prefrontal cortex in schizophrenia. GABA abnormalities are thought to play a role in cognitive impairments in the illness because of the central role of GABA in coordinating pyramidal cell activity. This study aimed to evaluate GABA levels in vivo in schizophrenia.

Methods: Sixteen unmedicated patients with schizophrenia, 16 medicated patients, and 22 healthy controls matched for age, sex, ethnicity, parental socioeconomic status, and cigarette smoking participated in this study. GABA levels were measured using proton MRS with a 3T GE Signa system and the J-edited spinecho difference method in the dorsolateral and medial prefrontal cortex (DLPFC and MPFC), normalized to the simultaneously acquired water signal. Working memory performance was assessed in all subjects.

Results: In the MPFC region, 30% elevations were found in GABA levels (p = .02) in unmedicated patients compared to controls. There were no alterations in the medicated patients, or in either group in DLPFC. No correlations with working memory performance were found.

Conclusions: GABA concentration measurements in unmedicated patients with schizophrenia showed elevations in MPFC but not DLPFC. Medicated patients did not show these elevations, suggesting possible normalization of levels with antipsychotic medication. GABA elevations were unexpected and suggest possible involvement of classes of interneurons not found to show impairments in postmortem studies.

Learning Objectives:
- Comparison of postmortem and in vivo data on GABA function in schizophrenia
- Effects of antipsychotic medication on the GABA system

Literature References:

DECREASED OCCIPITAL GABA IN ADULTS WITH TREATMENT-RESISTANT DEPRESSION

Sanjay Mathew, MD, Dikoma Shungu, PhD
Baylor College of Medicine, Houston, TX & Weill Cornell University, NY

While alterations in GABA and glutamate/glutamine have been reported in major depressive disorder, the relationship between treatment-resistance and these amino acid neurotransmitters is unexplored. This study used proton MRS to compare occipital cortex (OCC) and anterior cingulate cortex (ACC) GABA levels in 15 patients with treatment-resistant major depression (TRD), 18 patients with non-TRD MDD, and 24 healthy volunteers. Level of OCC GABA relative to voxel tissue water (W) were decreased in TRD compared with HV (20% mean reduction, p<0.001, Cohen's d=1.3) and non-TRD subjects (16% mean reduction, p=0.007, Cohen's d=1.4). There was a similar main effect of diagnosis for ACC GABA/W levels with TRD patients showing reduced GABA compared to the other groups. GABA results in OCC survived correction for multiple comparisons. In conclusion, our report provides evidence for a reduction in cortical GABA in patients classified as antidepressant medication resistant.

Learning Objectives:
- To understand the role of gaba in MDD
- To understand how MRS is used to quantify gaba

Literature References:
- Sanacora et al. Arch Gen Psych 2004; 61: 705-713.
GABA DEFICITS IN ADOLESCENT DEPRESSION: RELATIONSHIP TO ANHEDONIA

Vilma Gabbay1, MD, Xiangling Mao2, MS, Rachel G. Klein1, PhD, Benjamin A. Ely1, BS, James S. Babbs1, PhD, Carmen M. Alonso1, MD, Dikoma C. Shungu1, PhD

1New York University Child Study Center, New York, NY; 2Weill Cornell Medical College, New York, NY

Context: Anhedonia, a core symptom of major depressive disorder (MDD) and highly variable among MDD adolescents, may involve alterations in the major inhibitory amino acid neurotransmitter system of γ-aminobutyric acid (GABA).

Objective: To test whether anterior cingulate cortex (ACC) GABA levels, measured by proton magnetic resonance spectroscopy (1H MRS), are decreased in adolescents with MDD. The associations of GABA alterations with the presence and severity of anhedonia were explored.

Design: Case-control, cross-sectional study using single-voxel 1H MRS at 3T.

Setting: Two clinical research divisions at two teaching hospitals.

Participants: Twenty psychotropic medication-free adolescents with MDD (10 anhedonic, 12 females, ages 12-19) with episode duration ≥ eight weeks, and 21 control subjects, group-matched for gender and age.

Main Outcome Measure: ACC GABA levels expressed as ratios relative to unsuppressed voxel tissue water (w) and anhedonia scores expressed as a continuous variable.

Results: Compared to control subjects, MDD adolescents had significantly decreased ACC GABA/w (t = 3.2, p < 0.003). When MDD subjects were categorized based on the presence of anhedonia, only anhedonic patients had decreased GABA/w levels compared to control subjects (t = 4.08, p < 0.001, pcorr < 0.001). ACC GABA/w levels were negatively correlated with anhedonia scores for the whole MDD group (r = -0.50, p = 0.02), as well as for the entire participant sample including the control subjects (r = -0.54, p < 0.001). ACC white matter was also significantly decreased in MDD adolescents compared to controls (p = 0.04).

Conclusions: These findings suggest that GABA, the major inhibitory neurotransmitter in the brain, may be implicated in adolescent MDD and, more specifically, in those with anhedonia. In addition, use of a continuous rather than categorical scale of anhedonia, as in the present study, may permit greater specificity in evaluating this important clinical feature.

Learning Objectives:
- To understand the role of GABA alterations in adolescent depression, specifically in the symptom of anhedonia
- To understand the importance of using dimensional assessments of symptoms in conjunction with categorical diagnoses in biological investigations of psychiatric disorders.

Literature References:
- Sanacora, G et al. Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. Arch Gen Psych 2004; 61: 705-713.
PANEL OVERVIEW:
DSM-5 AND PSYCHOPATHOLOGY DOMAINS AS THERAPEUTIC INDICATIONS

William Carpenter¹, MD, Stephen Marder², MD, Robert Levin³, MD, Gregory Strauss⁴, PhD, Carlos Zarate⁵, MD

¹University of Maryland School of Medicine, ²UCLA, ³FDA, ⁴University of Maryland School of Medicine Maryland Psychiatric Research Center, ⁵National Institute of Mental Health

The DSM-5 Work Group on Psychotic Disorders is proposing a series of psychopathology domains to compliment disorder classification. Carpenter will describe the selected domains/dimensions and discuss them as therapeutic indications cutting across diagnostic boundaries. Marder will discuss implications of domains (rather than disorder class) as indications across diagnostic classes and implications for clinical trials methodology. Levin will present a view from the FDA on implications of this paradigm shift for regulatory functions. Strauss will present methodology for relating DSM-5 domains to NIMH RDoC behavior assessment/neural circuit paradigm. Zarate will open the discussion.

Learning Objectives:
- Gain knowledge of DSM-5 domains of pathology
- Understand implications for clinical trials and the NIMH RDoC initiative

PSYCHOTIC DISORDERS AND PSYCHOPATHOLOGY DOMAINS IN DSM-5

William Carpenter, MD
University of Maryland School of Medicine, Baltimore, MD

The DSM-5 Psychosis Chapter comprises several disorders that are heterogenous syndromes. Patients in a diagnostic class vary substantially in manifest psychopathology. This symptomatic heterogeneity can be addressed by ascertaining the psychopathology domains in each patient. To this end we propose a series of dimensions, each addressing a psychopathology domain.

This presentation will focus on these dimensions. These domains of psychopathology represent therapeutic needs from a clinical vantage, and are appropriate targets for drug discovery. As potential indications for regulatory approval, these dimensions cut across diagnostic boundaries and provide a new paradigm for therapeutic discovery.

Learning Objectives:
- Understand domains of pathology relevant to psychotic disorders
- Understand relevance of domains as therapeutic indications

Literature References:
- Peralta V and Cuesta MJ. How many and which are the psychopathological dimensions in schizophrenia? Issues influencing their ascertainment. Schizophrenia Research, 2001 Apr 30;49(3):269-85.
IMPLICATIONS OF CROSS-CUTTING DIMENSIONS FOR CLINICAL TRIALS METHODOLOGY

Stephen Marder, MD
UCLA, Los Angeles, CA

In 2002, Hyman and Fenton wrote that it may be unrealistic to expect a single pharmacological agent to be effective for all of the dimensions of a complex disorder such as schizophrenia. This is consistent with the observation that medications in psychiatry do not treat the disorders themselves, but treat symptoms that are “downstream” from the impaired brain functioning that causes the disorder. Moreover, illness dimensions that are reasonable targets for interventions may occur in a number of DSM diagnosed illnesses. Common dimensions that have received attention include: basic cognition and its components; social cognition; negative symptoms and components such as diminished expressiveness and apathy; excitement and agitation; depression; suicidal behaviors; diminished impulse control. This talk will review approaches for studying cognition and negative symptoms in schizophrenia trials and will speculate on how these approaches can be applied to other illness. Issues discussed will be developing measures for endpoints that characterize symptom dimensions; determining if the measures are appropriate across DSM disorders; developing preclinical models for each dimension; developing trial designs that can be applied within and across disorders; and addressing regulatory issues.

Learning Objectives:
- Attendees will gain a greater understanding of the symptom dimensions that can occur in multiple psychiatric illnesses.
- After viewing the presentation, attendees will understand the challenges in developing pharmacological agents for symptom dimensions that occur in multiple illnesses.

Literature References:

FDA PERSPECTIVE ON PSYCHOTIC DISORDERS AND SYMPTOM DIMENSIONS

Robert Levin, MD
FDA, Silver Spring, MD

DSM-V proposes an approach to psychotic disorders based on psychopathology domains and dimensions across the various psychotic disorders. It is possible that each domain/dimension could be a clinical research target as well as an indication for treatment. It will be important to discuss potential clinical study designs and related regulatory considerations for developing specific treatments. We will discuss examples of the approach cognitive dysfunction and negative symptoms associated with schizophrenia. We will discuss more broadly the opportunities and challenges in developing a dimensional approach across disorders. This will include a discussion of how to define clinical domain or entity, how to establish a valid measurement tool, would be useful study designs, and how to best analyze data in a clinical program based on cross-cutting domains and dimensions.

Learning Objectives:
- Participants will understand how the FDA views potential approaches to psychotic disorders based on domains or dimensions.
- Participants will understand how the FDA perspectives regarding categorical versus dimensional approaches may have different implications for clinical development programs.

Literature References:
RELATING SYMPTOM DIMENSIONS TO RDoC BEHAVIORS AND NEURAL CIRCUITS

Gregory Strauss PhD
University of Maryland School of Medicine Maryland Psychiatric Research Center, Baltimore, MD

Research in the areas of genetics and cognitive neuroscience are developing very rapidly; however, these developments have led to only modest gains in understanding and treating psychiatric disorders. One potential reason for this slow progress is that several diagnostic categories that appear to have a homogeneous clinical presentation have been found to be heterogeneous with regard to genetics and neural circuitry. The NIMH recently developed a strategic plan called the "Research Domain Criteria (RDoC)" that is designed to address some of the limitations associated with clinical diagnostic systems, with the ultimate goal of providing a research framework for classification based on empirical data from genetics, behavioral science, and cognitive neuroscience. Five RDoC domains have been proposed that are thought to cut across current DSM diagnostic categories: Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Systems for Social Processes, Arousal/Regulatory Systems. Each of these broad constructs can be examined across multiple classes of variables, including: genes, molecules, cells, neural circuits, physiology, behaviors, and self-reports. The DSM-V shift to dimensional classification has potential to interface well with the RDoC framework. However, the task of mapping current DSM dimensions onto RDoC domains may prove challenging. Here, we discuss how to translate DSM-5 psychopathology dimensions into behavioral assessments and neural circuit-level variables in relation to the RDoC framework, using examples of anhedonia and the positive valence system and anxiety and the negative valence system.

Learning Objectives:
- To learn about the purpose and focus of the RDoC framework
- To learn how to map DSM-V symptom dimensions onto the RDoC domains

Literature References:
PANEL OVERVIEW:  
TRAJECTORY-BASED DISEASE MODIFYING TREATMENTS IN PEDIATRIC PSYCHIATRY

John March1, MD, Christoph Correll2, MD, Craig Erickson3, MD, Kevin Gray4, MD, Benedetto Vitiello, MD

1Duke, 2Hofstra North Shore LIJ School of Medicine, 3Indiana University School of Medicine, 4Medical University of South Carolina, 5National Institute of Mental Health

Psychiatric illnesses are best conceptualized as neurodevelopmental disorders in which optimized carefully timed early intervention is the key to preemption defined as intervening early to preclude atypical development or to return an ill child to a normal developmental trajectory. Put another way, a greater understanding of neurodevelopment can lead to new and improved treatments that intervene early in the progression of a given illness phenotype thereby preventing symptoms from manifesting. In this context, the overall goal of this panel will be to examine the process and promise of developing novel disease modifying interventions for youth by first intent. To set the stage for disease-specific talks, Dr. John March will provide a broad overview of the necessary shift away from static interventions in adults to treatments based in translational developmental neuroscience, trajectory-based biomarker sciences in the form of companion diagnostics and surrogate endpoints, the process of experimental medicines development in youth, and the potentially important role of brain-computer interface devices in drug development. Dr. Christoph Correll will focus on disease modifying treatments in schizophrenia, with particular attention to intervening in the prodrome. Dr. Craig Erickson will focus on disease modifying treatments in autistic-spectrum youth, with particular attention to glutamatergic modulators. Dr. Kevin Gray will focus on disease modification in substance use disorders, with particular attention to early intervention with glutamatergic modulators in marijuana abuse/dependence. In his role as discussant, Dr. Benedetto Vitiello (NIMH) will discuss the four talks in the context of (1) the public-private partnerships that will be necessary to move a neurodevelopmentally-oriented non-adult research agenda forward and (2) the ethical issues involved in developing preemptive interventions in youth. Panel presentations will be appropriate for clinicians and researchers looking to deepen their knowledge of the active shift to experimental medicines development in youth.

DEVELOPING DISEASE MODIFYING TREATMENTS IN MENTALLY ILL YOUTH

John March, MD
Duke, Durham, NC

Given striking advances in translational developmental neuroscience and its convergence with developmental psychopathology and developmental epidemiology, it is now clear that mental illnesses are best thought of as neurodevelopmental disorders. This simple fact has enormous implications for the nature and organization of interventions for mentally ill children, adolescents and adults. After first defining preemptive and disease-modifying therapies, this presentation will provide a broad overview of the necessary shift away from static interventions in adults to treatments based in translational developmental neuroscience, trajectory-based biomarker sciences in the form of companion diagnostics and surrogate endpoints, the process of experimental medicines development in youth, and the potentially important role of brain-computer interface devices in drug development.

Learning Objectives:
- To understand shift to trajectory-based models of preemptive and disease-modifying interventions
- To understand the new landscape of intervention development in terms of the pivots to translational developmental neuroscience, biomarker sciences, novel learning-based, drug and device interventions

Literature References:

Learning Objectives:
- To understand the shift to trajectory-based models of preemptive disease-modifying interventions developed for youth by first intent
- To understand how this shift is taking place through three exemplary disorders: schizophrenia, autism, and marijuana abuse and dependence.
PREVENTION OF PSYCHOSIS: CURRENT APPROACHES AND FUTURE DIRECTIONS

Christoph Correll MD
Hofstra North Shore LIJ School of Medicine, Glen Oaks, NY

Primary and secondary prevention are preeminent goals for often severe and debilitating psychotic disorders. This is particularly relevant in children and adolescents, as pediatric-onset psychotic disorders generally have a more chronic and less responsive illness course than the adulthood-onset disease variant. The lack of a pathophysiologic understanding of psychosis limits the targeted search for novel interventions. However, over the past 15 years, the field has established valid criteria for indentifying youth and young adults who display symptoms and signs that significantly increase their risk for developing a psychotic disorder over the next 1-3 years. Results from longitudinal observational studies have fuelled a debate about the inclusion of the ‘attenuated psychosis syndrome’ in DSM-V. The first wave of controlled trials has provided preliminary evidence that fish oil, cognitive behavioral therapy, atypical antipsychotics, and integrated psychosocial interventions can prevent or delay the onset of psychosis compared to the control condition. However, except for one fish oil and one integrated psychosocial treatment trial, all other studies suggest that benefits are lost when the intervention is stopped. Endophenotypic characteristics of people at-risk for psychosis provide leads for next-generation interventions. These endophenotypes include disturbances in neurocognition, brain morphology, electrophysiology and neurochemistry. Moreover, results from prodromal and first episode samples and the fact that boundaries between the prodrome to schizophrenia and bipolar spectrum disorders are less clear support the notion that agents with anti-apoptotic, neuroprotective and neurogenesis promoting characteristics should be explored in phase 1 and phase 2 studies. However, since many putatively prodromal individuals are adolescents, ethical concerns about exposure to agents with unknown or potential risk for adverse effects during neurodevelopment have to be balanced against the potential benefits of such agents. Future research needs to focus on the transfer of approaches from bench to bedside, from controlled research to clinical settings and from general to staged and stratified interventions that balance the patient and treatment risk factors.

Learning Objectives:
- Describe the criteria for the prodrome to psychosis and the ‘attenuated psychosis syndrome’ proposed for DSM-V
- Review the clinical and biological risk markers for patients considered at clinical risk for psychosis
- Summarize the controlled efficacy data for interventions during the psychosis prodrome/clinical ultra-high risk phase
- Discuss novel treatment approaches for prevention of psychosis development

Literature References:

TARGETED TREATMENT DEVELOPMENT IN AUTISM SPECTRUM DISORDERS

Craig A. Erickson, MD
Indiana University School of Medicine, Indianapolis, IN

Recent autism research findings have begun to point to potential neurobiological factors that may present targets for autism drug development. Among potential drug targets in autism, recent emphasis has been given to investigation of agents impacting neuropeptide, glutamate, or gamma-aminobutyric acid (GABA) activity. In many cases, recent translational research findings have guided the choice of agents put forth for initial human targeted drug treatment study in autism. Targeted autism drug development would in theory potentially address the core social and communication impairments of the disorder, deficits not previously successfully targeted in pharmacotherapy trials. This drug development faces several challenges. Primary among these challenges is the heterogeneity of autism marked by variable presentation including the presence or absence of intellectual disability, functional speech, and epilepsy among other characteristics. An additional challenge relates to study design including selection of enrollment criteria and appropriate use of outcome measures focused on core impairments in targeted drug trials in autism. This presentation will review recent targeted drug development strategies in autism including review of translational research findings that support the use of various drug classes in this disorder. Challenges to study design in autism will additionally be reviewed including a look at potential future quantitative methods for assessing treatment response in this disorder.

Learning Objectives:
- The learner will develop an understanding of potential neurobiological targets of treatment in autism spectrum disorders.
- The learner will develop an understanding of the methods used to track potential improvement with treatment in persons with autism.

Literature References:
DISEASE MODIFYING TREATMENTS IN MARIJUANA DEPENDENCE

Kevin M. Gray, MD
Medical University of South Carolina, Charleston, SC

**Background:** Adolescents are especially prone to marijuana initiation, progression to dependence, and adverse consequences of use. To date, evidence-based marijuana cessation interventions in this critical developmental phase are lacking. While the development of aggressive treatments (including pharmacotherapy) is warranted, it must be done with sensitivity to concerns about safety, tolerability, and accessibility within this vulnerable age group. Balancing these needs and concerns, and in light of promising preclinical findings, we sought to investigate N-acetylcysteine (NAC), a glutamate-modifying over-the-counter supplement, as a marijuana cessation treatment in adolescents.

**Methods:** In an 8-week randomized controlled trial, treatment-seeking marijuana-dependent adolescents (N=116) were randomized to receive NAC 1200 mg or placebo twice daily, each added to brief weekly cessation counseling and a contingency management intervention. The primary efficacy measure was the odds of negative weekly urine cannabinoid tests during treatment among participants receiving NAC versus placebo, via intent-to-treat analysis. The primary tolerability measure was frequency of adverse events, compared by treatment group.

**Results:** NAC was well tolerated with minimal adverse events. NAC participants had more than twice the odds, compared to placebo participants, of submitting negative urine cannabinoid tests during treatment (OR = 2.4, [95% CI: 1.1-5.4], p = 0.021).

**Conclusions:** This is the first randomized trial of pharmacotherapy for marijuana dependence in any age group yielding a positive primary cessation outcome via intent-to-treat analysis. Findings support NAC as a pharmacotherapy to complement psychosocial treatment for marijuana dependence in adolescents. Given NAC's strong safety record in this age group and its inexpensive over-the-counter accessibility, further research is warranted to replicate these findings and to determine whether treatment with NAC during adolescence may alter long-term trajectories of marijuana and other substance use.

This research was supported by National Institute on Drug Abuse grant R01DA026777.

**Learning Objectives:**
- Recognize the need for improved adolescent-targeted marijuana cessation interventions
- Discuss the findings of a recent trial of N-acetylcysteine in marijuana-dependent adolescents

**Literature References:**
SPECIAL SESSION
12:30 P.M. - 2:30 P.M.

SPECIAL SESSION:
IMPROVING THE TEACHING-LEARNING PROCESS IN
PSYCHOPHARMACOLOGY: A DEMONSTRATION OF NEW TEACHING
FORMATS FROM THE ASCP PSYCHOPHARMACOLOGY CURRICULUM

Ira Glick, MD, Sidney Zisook, MD, Mark Rapaport, MD

1Stanford University School of Medicine, Stanford, CA 2University of California,
San Diego, 3Emory University School of Medicine

This year's teaching session will focus on the revised ASCP Psychopharmacology curriculum for psychiatric residents. Presenters will demonstrate 1) Dynamic and interactive lecturing, 2) making learning fun; e.g., using games, such as psychiatric Jeopardy, and 3) modernizing teaching by incorporating digital teaching tools. Each format each will be demonstrated – the aim is to have the audience-teachers leave with something new in their repertoire to bring back to their home institutions for teaching clinicians, residents, medical students and/or industry scientists.
WORKSHOP OVERVIEW:
FATIGUE ACROSS THE CNS SPECTRUM: SYMPTOM OR SIDE EFFECT

Steven Targum, MD, Maurizio Fava, MD, Thomas Wessex, MD, Larry Alphs, MD, Lynn Star, MD, Dana Hilt, MD, Michael Murphy, MD

'Clintara LLC, 'Massachusetts General Hospital, Berkshire Drug Development Consulting LLC, 'Janssen Scientific Affairs LLC, 'Envivo Pharmaceuticals, 'Worldwide Clinical Trials

Fatigue is a common symptom seen in many CNS disorders and a ubiquitous term that has multiple implications as used in everyday parlance. Consequently, the actual meaning attached to fatigue as a specific symptom can be ambiguous. The etiology of fatigue may be due to the disease of interest, to an unrelated co-morbid condition, to a treatment intervention (as a side effect), or simply the consequence of poor sleep quality.

Arnold (2008) described three distinct categories of fatigue that may occur in psychiatric patients: physical, cognitive, and emotional symptoms. The physical symptoms of fatigue include reduced activity, low energy, tiredness, decreased physical endurance, general weakness, sluggishness, and slowness. The cognitive symptoms include decreased concentration, decreased attention, decreased mental endurance, and slowed thinking. The emotional (affective) symptoms include decreased motivation or initiative (apathy), decreased interest, feeling bored or overwhelmed, and feeling low. Clearly, these diverse symptoms may be present in anybody at any time. Yet, persistent fatigue can yield medical, psychological, and social-occupational difficulties that may impede remission and have economic consequences.

Fatigue can be present as a consequential symptom or as a side effect of treatment intervention. Fatigue can be a reflection of both the physical and psychological aspects of a disorder, like multiple sclerosis or attention deficit disorder. Further, persistent fatigue as a residual symptom is often associated with a higher frequency of relapse, as in Major Depressive Disorder. In schizophrenia, fatigue must be differentiated from the core negative symptoms, from depression, and from sedating treatment interventions. Finally, unresolved fatigue can be a major problem in the workplace, at school, and at home. In this workshop, we will address the behavioral and health outcome ramifications of fatigue across the CNS spectrum and in non-psychiatric patients as well.

Learning Objectives:
- Describe the various components of fatigue seen in different psychiatric or neurologic patients
- Discern between the constellation of fatigue symptoms as a disease related or side effect
- Explore the behavioral and health ramifications of residual fatigue
- Explore treatment options to deal with fatigue as part of a psychiatric or neurological disorder

INTRODUCTION: THE MANY FACES OF FATIGUE

Steven D. Targum, MD
Clintara LLC, Boston, MA

Symptoms of fatigue occur in everyday life but are also seen in many medical disorders, and particularly in psychiatry and neurology. Fatigue can be part of the symptom complex of the disorder of interest, related to a co-morbid condition, a consequence of treatment (side effect), or simply due to poor sleep quality or stress. Fatigue can be a residual symptom that persists despite treatment of the underlying disorder. There is high likelihood that patients with persistent fatigue will have work and/or social performance difficulties, related health problems, and in some disorders (like Major Depressive Disorder) may relapse sooner than patients who do not complain of fatigue.

The term fatigue is a broad concept that conveys many meanings. Arnold (2008) delineated three categories of fatigue reflecting physical, cognitive, and emotional dimensions. The physical symptoms of fatigue include reduced activity, low energy, tiredness, decreased physical endurance, increased effort to do physical tasks and with overcoming inactivity, general weakness, heaviness, slowness or sluggishness, non-restorative sleep, and sleepiness. The cognitive symptoms include decreased concentration, decreased attention, decreased mental endurance, and slowed thinking. The emotional (affective) symptoms of fatigue include decreased motivation or initiative (apathy), decreased interest, feeling overwhelmed, feeling bored, aversion to effort, and feeling low.

This workshop will explore the impact and relevance of fatigue across the CNS spectrum.

Learning Objectives:
- Describe the different symptoms associated with fatigue
- Explore the interplay between fatigue and different CNS disorders
- Describe the social and health consequences of persistent fatigue

Literature References:
- Arnold LM. Understanding Fatigue in Major Depressive Disorder and Other Medical Disorders. Psychosomatics 2008; 49:185–190.
**Fatigue Associated with Major Depressive Disorder**

Maurizio Fava, MD

Massachusetts General Hospital, Boston, MA

Patients with major depressive disorder (MDD) commonly experience fatigue. Fatigue can be, in some cases, a prodromal symptom of MDD as well, and has been shown to be one of the most common symptoms of MDD. Fatigue may persist despite effective antidepressant treatment, or may emerge as adverse effect of some antidepressant treatments. Traditional measures of fatigue focus primarily on the more physical aspects of fatigue and fail to include other dimensions of fatigue, such as cognitive and affective symptoms. The cognitive aspects of fatigue include decreased concentration and attention, and slowed thinking, while the affective symptoms include decreased motivation or initiative. In fact, a study from our group has clearly shown that fatigue is significantly associated with inability to focus, alertness, and feeling “blue”. Recent studies have shown the usefulness of measures that do capture a broader range of fatigue-related symptoms. Given the importance and prominence of fatigue in MDD, it has become evident that antidepressant treatments need to place a greater focus on fatigue as a way of reducing the chances of significant residual symptoms and subsequent risk of relapse. Currently available therapies do not adequately address this problem, as fatigue is one of the two most common residual symptoms of depression among MDD patients who have remitted during antidepressant therapy. A number of augmentation strategies can be employed to target fatigue, but the efficacy of these augmentation strategies must be researched further.

**Learning Objectives:**
- To become familiar with the symptoms of fatigue commonly reported by patients with major depressive disorder
- To understand the relationships between fatigue and other depressive symptoms

**Literature References:**

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**Fatigue Associated with Neurological Disorders: Focus on Multiple Sclerosis**

Thomas Wessel, MD

Berkshire Drug Development Consulting LLC, Lenox, MA

Fatigue is a common and vexing problem for many patients with different neurological diseases and has been a particular focus of MS research in recent years. Many MS patients rate fatigue as the single most troubling symptom of their disease and on occasion fatigue will precede the diagnosis. Severe fatigue was reported in 74% of participants in a recent NARCOMS survey (Hadjimichael et al, 2008). Fatigue occurs in all subtypes of MS and appears to be related to lesion burden in the central nervous system and the accumulating impairment. One hallmark of fatigue in MS is the pronounced sensitivity to heat (Krupp et al, 1989). The contribution of intrinsic disease-specific causes for fatigue may be difficult to distinguish from such factors as concomitant medical disease and drug effects on one hand or depression, anxiety and sleep disturbances on the other hand. A number of self-reported and performance-based instruments are available for the purpose of monitoring individual patients or as research tools in the clinical trial setting. These instruments vary from simple single-item visual analog scales to more complex questionnaires that divide items into separate groupings or sub-scales. The recent development of Clinical Global Impression of Severity (CGI-S) and Patient Global Impression of severity (PGI-S) for Fatigue instruments focuses specifically on targeted symptoms of fatigue and provides enhanced scoring precision. Recent research studies have demonstrated that these customized CGI-S and PGI-S instruments for fatigue are reliable measures of fatigue in psychiatric patients and MS patients alike and are highly correlated.

**Learning Objectives:**
- Fatigue in neurological diseases
- Prevalence and symptomatology of fatigue in MS
- Medical and psychiatric causes for fatigue in MS patients
- Assessment tools and clinical trials for fatigue in MS

**Literature References:**
DIFFERENTIATING NEGATIVE SYMPTOMS FROM FATIGUE AND OTHER COMORBID CONDITIONS IN SCHIZOPHRENIA

Larry Alphs, MD
Janssen Scientific Affairs LLC, Titusville, New Jersey

The costs of treating schizophrenia and the loss in patients' productivity are estimated to be as high as $60 billion annually in the United States. Research suggests that negative symptoms of schizophrenia contribute significantly to these costs and to poor functional outcomes. Nevertheless, negative symptoms remain inadequately treated.

Development of better treatments for negative symptoms requires that they be clearly differentiated from symptoms with overlapping phenotypes, so that putative treatments will be correctly targeted and study results appropriately interpreted. Negative symptoms share behavioral and psychological phenotypic characteristics with fatigue, depression, and related side effects of medications.

This presentation will identify phenotypic overlap among negative symptoms, fatigue, depression, and medication-mediated drowsiness/sleepiness and will suggest how these constructs can be differentiated from one another. Study designs, endpoints, and scales that facilitate symptom differentiation will be discussed. In particular, the NSA-16 will be reviewed as one instrument that—combined with the appropriate design and analytic approaches—can be useful in untangling the complex interplay of these signs and symptoms.

Learning Objectives:
- To describe the indicators of the negative symptoms of schizophrenia.
- To differentiate the negative symptoms of schizophrenia from those of fatigue, depression and medication side effects.

Literature References:

ADHD AND FATIGUE

Lynn Starr, MD
Janssen Scientific Affairs LLC, Titusville, New Jersey

Overlap in symptoms associated with cognition in attention-deficit hyperactivity disorder (ADHD) and fatigue syndromes such as chronic fatigue syndrome and fibromyalgia have been reported. This overlap appears to be most pronounced in the areas of disruptions in attention and memory, while disturbances in sleep are another common feature.

It is unclear, however, whether fatigue in ADHD is a result of ADHD symptoms, disruptions in sleep, pharmacotherapy treatment, or a consequence of other features. Some have postulated that ADHD is associated with hypoarousal and a fundamental impairment in arousal regulation. 2

This discussion will describe the overlap in symptoms seen in ADHD and fatigue syndromes, review patterns of sleep disruption and results of pharmacological treatment for ADHD, and outline the costs of fatigue in this disorder. Emphasis will be placed on the importance of evaluation of fatigue symptoms and the impact of treatment strategies for ADHD.

Learning Objectives:
- To explore the symptoms of fatigue in ADHD.
- To review the impact of available ADHD treatments on symptoms.
- To assess the larger implications of hypoarousal in this disorder.

Literature References:
FATIGUE AND ALZHEIMER’S DISEASE

Dana Hilt, MD
Envivo Pharmaceuticals, Watertown, MA

Fatigue in Alzheimer’s Disease: Risk factor, diagnostic confound, or treatment target?

Fatigue is often observed in an elderly population. However, fatigue has rarely been studied as a specific symptom/risk factor in patients with Alzheimer’s disease (AD). Symptoms of fatigue may be indicators of other underlying pathologies including endocrinopathies, sleep disorders, depression, or other comorbidities. These conditions may either be risk factors for AD or confounding diagnostic factors. For instance, sleep apnea and other sleep disturbances may be risk factors for the development of AD as well as depression in elderly subjects. Sleep/circadian disturbances characterized by nocturnal hyperarousal and agitation may be accompanied by excessive daytime sleepiness and fatigue and therefore complicate the diagnosis and treatment of AD patients. Depressed mood, lassitude, irritability, and fatigue are among the most common symptoms of both depression and AD in the elderly. Consequently, symptoms of fatigue may make the accurate assessment of cognition in AD patients difficult especially if accompanied by depression. Approaches to the systematic evaluation of fatigue in AD patients, its underlying potential causes(s), and potential response to therapies will be discussed. Specific questions for future research will be posed including optimal metrics for assessing fatigue and whether fatigue is a symptom whose specific treatment can improve AD patient function. Finally, the impact of caregiver fatigue will be briefly discussed.

Learning Objectives:
- Summarize the diagnostic significance of fatigue as a symptom in AD
- Provide a diagnostic and therapeutic framework for assessment of fatigue

Literature References:

HEALTH OUTCOME ISSUES RELATED TO RESIDUAL FATIGUE

Michael F. Murphy, MD
Worldwide Clinical Trials, King of Prussia, PA

Neither orderly nor rational, the healthcare environment presents a mosaic of providers, products, services, and intermediaries mediating healthcare shaped by economic constraints as much as clinical care conventions and regulatory guidance. Correspondingly, information required for informed healthcare decisions varies appreciably by the audience, the therapeutic area, the intervention, and the stage of product development. The impact of disease burden and technology on a system of care (in addition to the patient) thus becomes a significant influence on clinical research activities during the transition from the bench to the physician-patient-payer interface.

In particular, there is an emerging interest in the assessment of fatigue in relationship to healthcare outcomes either as a component of a disease state or as an adverse effect related to treatment. Catalysts for inquiry are as diverse as the audience, but primarily revolve around observations that individuals with fatigue as a major component of a clinical presentation are high consumers of healthcare, high consumers of specialty care driven by somatic complaints, and are more prone to be noncompliant with therapy resulting in longer-term adverse clinical outcomes.

Within a clinical development program, both observational and interventional studies provide insight to healthcare outcomes which have a genesis in residual fatigue states. Issues related to analyses (e.g., cost benefit, cost-effectiveness, cost-minimization), the type of outcomes to be accessed (direct medical, direct nonmedical, productivity, and intangible) and the perspectives from which the data will be analyzed are overarching considerations. The proportion of total cost collected in a study, the delivery settings where data are collected, healthcare utilization occurring in non-study sites, and the clinical characteristics of study subjects actually providing data often are key parameters.

Multiple stakeholders need actionable information based upon these data. For example, self insured employers wish to know whether a more expensive product associated with fatigue justifies inclusion on the formulary, and the impact of disease or treatment-related fatigued on absenteeism and presenteeism (on job impairment). Providers of commercial insurance wish to demonstrate that they are responsive to the concerns of enrollees with disease related fatigue and that expensive therapy with fatigue as an adverse effect has appropriate trade-offs when utility is considered broadly. Both physicians and patients seek better compliance with therapy and enhanced quality of life, yet residual fatigue adversely impacts both. Diseases as diverse as schizophrenia, depression, multiple sclerosis and ADHD offer illustrative case studies.

Learning Objectives:
- Evaluate fatigue secondary to disease or treatment from the perspectives of multiple stakeholders
- Examine methodology for the assessment of healthcare outcomes secondary to residual fatigue and related symptoms

Literature References:
WORKSHOP OVERVIEW:
PSYCHOSOCIAL TREATMENT PLATFORMS IN PSYCHOPHARMACOLOGY RCTS

Nina Schooler1, PhD, Stephanie S. O’Malley2, PhD, Michele Levine3, PhD, Ellen Frank4, PhD, Dawn Velligan5, PhD
1SUNY Downstate Medical Center, 2Yale University School of Medicine, New Haven, CT, 3University of Pittsburgh School of Medicine, Pittsburgh, PA, 4University of Texas Health Science Center, San Antonio, San Antonio, TX

Randomized Clinical Trials (RCTs) of psychosocial (PS) treatments in mental health & substance use disorders often specify allowed medications & a medication platform on which treatment will be delivered. In contrast, in psychopharmacology (PP) RCTs for mental health disorders, specification of PS treatment is rare. In multi-center RCTs there may be enormous variability. The unstated assumption underlying this lack of control may be that the clinical & PS environment is a small source of variance that can be considered a part of error variance.

We will consider an alternative assumption. PS treatment & context are an important source of outcome variance & defining a platform or limiting PS treatment can reduce error variance in PP RCTs & enhance signal detection. We will review RCTs in which platforms have been specified & consider how these models can be applied more broadly than they have been to date. The workshop includes people who have extensive experience in utilizing such platforms and others with experience in design and conduct of RCTs of psychosocial treatment. This is a valuable mix and should promote informed discussion. We will allot ample time for discussion after each of the more formal presentations and also at least 45 minutes to consider the last learning objective - namely how can we move forward to develop and assess such platforms, as well as whether platforms need to be disorder- or treatment-specific or whether some platforms that address common issues can be developed.

We will address:
1. Potential utility of specification of PS treatment platforms in PP RCTs,
2. Instances in which there has been specification & limitation of PS treatment in alcohol & nicotine use PP RCTs
3. Models for PS platforms in mental health disorders; focusing on schizophrenia & mood disorders

Speakers have extensive experience with PS & PP RCTs. They also work in a range of the brain diseases than NCDEU now addresses

Learning Objectives:
• Know the current status of psychosocial treatment platforms in psychopharmacology RCTs across a range of CNS disorders
• Understand limitations & advantages of specifying a psychosocial platform in psychopharmacology RCTs consider steps needed to develop & assess platforms in psychopharmacology RCTs

PSYCHOSOCIAL TREATMENTS IN RCTS FOR ALCOHOL DISORDERS

Stephanie S. O’Malley PhD
Yale University School of Medicine, New Haven, CT

Pharmacotherapy trials for alcohol dependence now generally incorporate a specified behavioral platform for delivering treatments. The general goals of these approaches are to ensure comparability of treatment across sites and treatment arms, encourage medication adherence, support the patient’s efforts to change their drinking behavior and provide treatment of sufficient intensity so as to be consistent with ethical practice. Treatment approaches that can be broadly generalized to nonspecialty settings where individuals with alcohol dependence are likely to present, such as primary care, are often recommended. In the alcohol field, the degree to which the treatment promotes attendance at support groups (e.g., Alcoholics Anonymous) or permit additional sessions may inadvertently undermine the goal of comparable treatment across conditions and differentially improve the functioning of patients in the placebo condition. Other critical factors are whether the goal of treatment is abstinence or moderated drinking and the minimal level of behavioral treatment that can be provided. Each of these issues will be discussed and illustrated with data from completed studies.

Learning Objectives:
• To learn about standardized behavioral platforms for alcoholism pharmacotherapy studies.
• To learn how an understanding of the anticipated effects of the medication on drinking could influence the goals of the behavioral treatment, related to alcohol abstinence or moderation.

Literature References:
PSYCHOSOCIAL TREATMENT IN RCTS OF MEDICATIONS FOR SMOKING CESSATION

Michele Levine, PhD
University of Pittsburgh School of Medicine, Pittsburgh, PA

Medication use in Psychosocial treatments for smoking cessation: Bupropion and Cognitive Behavioral Treatment for Weight Concerns

Pharmacologic interventions in the treatment of smoking cessation have become increasingly common, and are more effective when combined with cessation counseling. However, issues related to the management of medication during the conduct of smoking cessation clinical trials are not well defined. Using the example of a trial in which we tested the combination of a cessation medication and two different adjunctive approaches for smoking cessation, we will examine the ways in which pharmacotherapy is implemented and evaluated. In this randomized, double-blind, placebo-controlled trial, women smokers concerned about postcessation weight gain (n = 349) received smoking cessation counseling and were randomized to one of two adjunctive interventions: CONCERN or STANDARD, and one of two medication conditions: bupropion (B) or placebo (P) for 6 months. Weight-concerned women smokers receiving the combination of CONCERN+B were most likely to sustain smoking abstinence. Moreover, bupropion improved abstinence rates among those receiving the CONCERN intervention, but did not confer significant benefit during the period of active drug treatment for those receiving the STANDARD adjunct. This study also highlights the importance of attendance at treatment sessions in smoking cessation trials combining drugs and psychosocial treatment as women in CONCERN+B attended more intervention sessions than those in CONCERN+P. Lessons learned about combination of medication and counseling for smoking cessation intervention, as well as questions for future research will be discussed.

Learning Objectives:
- Understand the ways in which psychosocial and pharmacologic interventions can be applied to smoking cessation
- Increase understanding of the characteristics of psychosocial interventions that can be used in smoking cessation trials

Literature References:

CHARACTERISTICS OF PSYCHOSOCIAL TREATMENT PLATFORMS FOR RCT’S IN MOOD DISORDERS

Ellen Frank, PhD
University of Pittsburgh School of Medicine, Pittsburgh, PA

We have often argued that there will not be a true test of the efficacy of pharmacotherapy alone for mood disorders until medications can be dispensed from ATM machines. As long as a human being is involved in the dispensing of medication, there will be non-specific factors present in the clinical encounter that, in the case of mood disorders, can have a pronounced effect on outcome. The model psychosocial treatment platform for RCTs in mood disorders was developed, in a direct effort to systematize and equate those non-specific effects across active and placebo conditions, by Fawcett and colleagues for the NIMH Treatment of Depression Collaborative Research Project (TDCRP). The TDCRP model, consisting primarily of psychoeducation, careful assessment of both therapeutic and collateral effects and an empathic stance on the part of the clinician, has been followed to a greater or lesser extent by almost all federally- and foundation-funded investigators in mood disorders since that time. Of note, not only was pharmacotherapist behavior specified in a well-written manual in TDCRP, it was monitored via audiotape. In contrast, pharma-sponsored trials have rarely specified the treatment platform on which medication and placebo are to be dispensed or monitored clinician behavior, perhaps accounting for the increasingly frequent failure of those trials. This presentation will review the various psychosocial treatment platforms used in mood disorder RCTs over the last several decades and attempt to relate the nature of those platforms to the relative success of the trials.

Learning Objectives:
- Achieve familiarity with the nature of psychosocial treatment platforms used in RCT’s for mood disorders
- Understand the impact of specification of the treatment platform and direct observation of clinician behavior on study outcomes

Literature References:
ADHERENCE ENHANCEMENT AS A PSYCHOSOCIAL PLATFORM FOR PSYCHOPHARMACOLOGY RCTS

Dawn Velligan, PhD
University of Texas Health Science Center, San Antonio, TX

Placebo response rates for seriously mentally ill patients participating in clinical drug trials have increased substantially over the past decade. Moreover, in some trials, participants in the placebo conditions have been found to have blood levels indicating that they have taken an active medication. In the past, while many studies were conducted in inpatient settings allowing all doses of medication to be observed, current trials are primarily conducted on an outpatient basis. A typical strategy to assess adherence in such trials involves counting pills from bottles brought into the research center at each visit. A psychosocial platform for monitoring and improving medication adherence would be important to consider in designing clinical trials. Such a platform could potentially include 1) ensuring that a home visit is made at the beginning of randomization to identify current medications available to the patient and to bag and staple these medications with a notice asking the patient not to take them during the trial. During this visit, environmental supports such as alarms, signs and the placement of medication could be utilized to encourage regular adherence during the trial 2) regular home visits to count medication and ensure that non-trial meds have not been taken (seal not broken on the bag) 3) daily home visits to directly observe all medication doses. While some of these measures may add cost to the trial and involve greater time commitments on the part of the participants as well as the research organization, the cost may be offset by savings that result from needing fewer participants to find separation between the study medication and comparator treatments.

Learning Objectives:
- Identify consequences of poor adherence to study medication in clinical trials
- Describe a psychosocial platform to increase adherence during clinical trials
- Evaluate the pros and cons of utilizing a standard psychosocial platform to improve adherence in clinical trials

Literature References:
- Kemp et al, What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it? Schizophrenia Bulletin 2010; 36, 505-509.
WORKSHOP OVERVIEW:
COMPARATIVE EFFECTIVENESS TRIALS IN BIPOLAR DISORDER: WHAT HAVE WE LEARNED AND WHERE DO WE NEED TO GO FROM HERE?

Terence Ketter1, MD, Andrew Nierenberg2, MD, Michael E. Thase1, MD, Joseph Calabrese3, MD
1Stanford, Stanford, CA, Massachusetts General Hospital, Harvard University, 2University of Pennsylvania, Philadelphia, PA, 3Case Western Reserve University, Cleveland, OH

Efficacy trials in bipolar disorder commonly fall short of informing real-world clinical decisions due to multiple design characteristics (e.g., restrictive inclusion and exclusion criteria, exclusion of additional medications, and use of double-blind placebo-controlled designs) that serve to enhance assay sensitivity but limit generalizability. To fill the gap between clinical efficacy trials and the need to inform clinical comparative effectiveness (CE), within the past decade, researchers conducted several key trials, including STEP-BD, BALANCE, LITMUS, and currently CEQUEL and CHOICE. These were designed to inform clinical care, assess predictors, moderators, and mediators, and provide platforms to assess biomarkers such as pharmacogenetics.

Some of these CE studies allowed for flexible treatment with non-study medications to reflect real-world clinical approaches and retain patients, resulting in not only new research opportunities, but also challenges in interpreting results (e.g., how were outcomes related to study as opposed to non-study medications?). New metrics have been developed to assess novel outcomes (e.g., number of medication changes) beyond standard mood symptom/episode metrics. In this Workshop, presenters will briefly discuss the designs and relevant outcomes, if available, of several key bipolar CE studies. This will be followed by a group discussion of the strengths and limitations of these approaches, and future needs and opportunities.

Learning Objectives:
- Appreciate the variety of designs of comparative effectiveness trials in bipolar disorder
- Recognize the trade-offs involved in balancing the needs for generalizability and assay sensitivity in comparative effectiveness trials in bipolar disorder
- Understand the strengths and limitations of outcome measures used in comparative effectiveness trials in bipolar disorder

DESIGN CONSIDERATIONS IN BIPOLAR DISORDER COMPARATIVE EFFECTIVENESS RESEARCH

Michael E. Thase, MD
University of Pennsylvania, Philadelphia, PA

Comparative effectiveness research differs from so-called efficacy research in several important ways. Perhaps most importantly, interventions being contrasted in comparative effectiveness research typically have established efficacy and, as such, a placebo control group is not necessary. Resources can thus be concentrated on the randomized comparison of two - or sometimes three - useful strategies. Another characteristic is that the study group should readily generalizable to nonresearch populations with the disorder of interest, which is facilitated by adopting broad inclusion criteria and relatively few exclusion criteria in addition to not utilizing a placebo control group. Sometimes comparative effectiveness researchers also opt to use “open” (unblinded) delivery of study treatments and patient reported outcome measures to further enhance generalizability. One consequence of these design choices is that the magnitude of the expected difference between a “good” treatment and a potentially “better” one is likely to be relatively modest (e.g., 10-20%), necessitating a large sample. Even larger samples are needed when the aim of the comparative effectiveness study is to test noninferiority. Healthcare utilization and cost data can provide critical data to help weigh the cost-effectiveness of the treatments of interest. Examples of comparative effectiveness research conducted to date in bipolar disorder will be drawn upon to illustrate key points.

Learning Objectives:
- The learner will be able to compare and contrast the research designs used in efficacy and effectiveness research.
- The learner will be able to weigh the strengths and limitations of the comparative effectiveness studies conducted to date in bipolar disorder.

Literature References:
BALANCING GENERALIZABILITY AND ASSAY SENSITIVITY NEEDS IN BIPOLAR DISORDER COMPARATIVE EFFECTIVENESS RESEARCH

Joseph R. Calabrese MD
Case Western Reserve University, Cleveland, OH

Drug development in bipolar disorder (BD) is complicated by high rates of lifetime comorbidity (Merikangas et al 2007), which places patients at high risk for suicidality (Nock et al 2010). Pharma drug development begins with a lesser challenge of conducting of efficacy studies, which prioritize internal validity (assay sensitivity) at the expense of external validity (generalizability). Once efficacy is established, there exists a need to move forward on the continuum of improved generalizability by studying more heterogeneous subgroups (anxiety, substance abuse, metabolic burden). Efficacy studies are allowed to artificially inflate effect size by excluding hard-to-treat patients, whereas effectiveness studies deflate effect size by including them. The field attempts to manage this heterogeneity by increasing sample size, but sample sizes continue to be modest due to pragmatic considerations. Therefore, everything done by Pharma is just a beginning and no one drug development effort is ever good enough because numerous subgroups exist in BD. The challenge for the field is how fast to we move forward on this continuum of improved generalizability and how do we do so without compromising assay sensitivity. This presentation will contrast the methodological features used in recent research to manage these challenges, including the first generation of BP depression studies, STEP-BD, LIITMUS, BALANCE, and CHOICE studies.

Learning Objectives:
- Understand the magnitude of the unmet need in the design and conduct of more inclusive bipolar study populations.
- Understand the methodological features used in recent studies to improve study generalizability without fatally sacrificing assay sensitivity.

Literature References:
- Nock M, et al. Mental disorders, comorbidity and suicidal behavior: results from the NCS-R.

OUTCOME MEASURE STRENGTHS AND LIMITATIONS IN BIPOLAR DISORDER COMPARATIVE EFFECTIVENESS RESEARCH

Terence Arthur Ketter, MD
Stanford University, Stanford, CA

Comparative effectiveness trials for bipolar disorder strive to assess long-term treatments with participants more closely representing those in clinical practice. To date, outcomes have been primarily based on mood symptoms/episodes. Thus, STEP-BD emphasized recovery (achieving 8 weeks of remission) and episode-based relapse (emergence of new mood episode), BALANCE focused on intervention-based relapse (initiation of new intervention for emergent mood episode), LIITMUS used the Clinical Global Impression for Bipolar Disorder-Overall Illness Severity, while CEQUEL is using remission, and CHOICE is using the CGI Efficacy Index (incorporating both mood and side-effects). However, co-primary outcomes looking beyond mood symptoms/episodes are evolving. For example, in the Bipolar Trials Network LIITMUS and CHOICE studies were designed to mirror practice with clinicians instructed to treat symptoms or side effects that troubled participants. As a consequence, post-baseline illness severity was expected to affect treatment and treatment was expected to affect severity, yielding problematic reciprocal causation. To address this challenge, the innovative co-primary outcome measure Necessary Clinical Adjustments (NCAs), was used as a proxy for overall effectiveness of treatment. NCAs represent a count of modifications of all medications prescribed in response to symptom severity, inadequate function, or side effects, but not based on positive responses. The BTN bi-dimensional approach is hypothesized to better reflect patient and provider clinical experiences than outcomes solely based on mood symptoms/episodes. In conclusion, in order for comparative effectiveness trials to inform clinical practice, trials must carefully consider implications of the outcome measure(s) used.

Learning Objectives:
- Understand the strengths and limitations of outcome measures used in comparative effectiveness trials in bipolar disorder
- Appreciate the potential contributions of outcomes looking beyond mood symptoms/episodes.

Literature References:
WORKSHOP OVERVIEW:
MODERATORS AND MEDIATORS OF TREATMENT OUTCOME IN LATE LIFE DEPRESSION

Craig Nelson1, MD, Warren Taylor2, MD, D. Devanand2, MD, Faith Gunning-Dixon2, PhD, R. Mackin3, PhD

1UCSF, 2Duke University School of Medicine, Columbia University, Weill Cornell Medical College

Depression is a common psychiatric disorder in older adults that causes suffering and disability, and aggravates the course of medical illnesses. Antidepressants have been the mainstay of treatment for late life depression but recent meta-analyses indicate that the advantage of antidepressants relative to placebo is reduced. This workshop will examine factors that moderate antidepressant response in older adults and then begin to explore processes that may mediate these effects. Craig Nelson, M.D. will review recent meta-analyses of antidepressant efficacy in late life major depression that reveal modest antidepressant efficacy. A patient-level meta-analysis will be examined to determine factors that moderate more robust drug effects and identify subgroups for whom antidepressants lack efficacy. Steven Roosen, M.D. will review the concepts of executive dysfunction and vascular depression and the impact on treatment response. He will review the available data that suggests the criteria used for defining VD and ED significantly influence response rates. While executive dysfunction and vascular disease have received considerable attention, depression is common with patients with Alzheimer's disease. D. P. Devanand, M.D. will review the prevalence of depression in Alzheimer's dementia. He will present a meta-analysis of antidepressant trials and review a large trial recently reported in this patient group. He will also describe two pilot studies of cognitive enhancer augmentation in depressed patients with cognitive impairment. Faith Gunning-Dixon, Ph.D. will use a combination of structural and fMRI methods to examine abnormalities in cognitive control and emotional regulation networks that characterize late-life depression and are associated with persistence of the illness despite antidepressant treatment. In addition, she will explore the role of cerebrovascular disease and vascular risk factors on these cerebral networks. Scott Mackin, Ph.D. will continue this exploration examining cerebral perfusion in depressed patients using arterial spin labeling on MRI. He will also describe cortical thinning found in these patients and how these changes may elate to cognitive disturbance in older depressed patients.

Learning Objectives:
• The participant will recognize moderators of response
• Will describe potential mediators of response

EFFICACY OF ANTIDEPRESSANTS IN LATE LIFE DEPRESSION AND MODERATORS OF RESPONSE

Craig Nelson, MD
UCSF, San Francisco, CA

Major depression is a common disorder in older adults that causes suffering, reduces quality of life, impairs functioning, and aggravates the course of medical illness (1). Antidepressants are the primary treatment for late life depression but their efficacy has been questioned. In a prior systematic review and trial level meta-analysis we found 10 placebo-controlled random assignment trials of second generation antidepressants in community dwelling patients aged 60 years and older (2). Antidepressants were more effective than placebo (odds ratio = 1.40, 95% CI 1.24 to 1.57, z = 5.45, p = 0.0001); however, the magnitude of the drug-placebo difference was modest resulting in a NNT of 11. This analysis raised the question of whether moderators of response could be determined that would help to identify individuals with a more robust response or those who were unlikely to benefit from treatment. The manufacturers of the antidepressants studied in the prior 10 trials were contacted and individual patient data was requested for a limited number of variables. The variables selected were those suggested in the literature as associated with response and those commonly collected in clinical trials. The variables were age, sex, age of onset, course (single episode/recurrent), and baseline severity. These data were obtained for all of the 10 trials. Nine of the trials included a SSRI. Venlafaxine, duloxetine, and bupropion were each included in one trial. The trials included 4141 patients (2500 women and 1641 men) of whom 2360 received drug treatment and 1781 received placebo. Response was defined as 50% or greater improvement on the Hamilton Depression Rating Scale or the Montgomery Asberg Depression Rating Scale. Logistic regression was performed to examine the association of each of the variables of interest with response and with the treatment group-response interaction (the latter reflects the association with the drug-placebo difference) while controlling for study. Early age of onset was significantly associated with a greater drug-placebo difference. Alternatively antidepressants were not more effective than placebo in patients 75 years or older. Among this latter advanced age group, early onset did identify a subgroup that was drug responsive. Older patients with late onset depression may include a disproportionate number of individuals with underlying vascular disease or pre-clinical Alzheimer's disease.

Learning Objectives:
• Participants will be able to describe the efficacy of antidepressants in late life depression
• Will be able to identify older depressed patients who will and will not benefit from antidepressant treatment

Literature References:
Efficacy of Antidepressants in Older Depressed Patients with Vascular Depression and/or Executive Dysfunction Arterial Vascular Depression

Warren Taylor, MD
Duke University School of Medicine, Durham, NC

There are many studies that report that patients with vascular depression (VD) and/or executive dysfunction (ED) respond to antidepressants at a lower rate than patients without these characteristics. However, the response rates vary considerably depending on the definition of vascular depression or the test used to establish the presence of ED. Furthermore responding at a lower rate does not mean that antidepressants are not the first line treatment in the clinical situation. This presentation will review the studies on response rates in patients with VD and ED and what these data mean to the clinician. Finally these clinical pictures will be linked with the underlying pathophysiology demonstrating directions for the investigation of new therapeutic approaches.

Learning Objectives:
- Review the definition of vascular depression
- Review the definition of executive dysfunction
- Review response to antidepressants in this patient population
- Review how pathophysiological mechanisms contributing to vascular depression may serve as novel therapeutic targets.

Literature References:

Efficacy of Antidepressants in Older Depressed Patients with Alzheimer's Disease and the Potential for Augmentation with Cognitive Enhancers in Depressed Patients with Cognitive Impairment

D. P. Devanand, MD
Columbia University, New York, NY

Treatment of Depression and Cognitive Impairment in the Elderly

Approximately 10 to 35% of the elderly have depressive symptoms, and 10 to 40% of the elderly have cognitive impairment. Patients presenting with both depression (DEP) and cognitive impairment (CII), DEPCI, represent a unique, understudied population that is difficult to diagnose, treat and estimate prognosis. In DEPCI, there is a lack of data on treatment response of mood symptoms to antidepressant treatment, and particularly of cognitive deficits to cognitive enhancer treatment. Further, the long-term prognosis remains unclear. In a pilot study, we found that donepezil was superior to placebo in improving memory performance and decreasing conversion rate to dementia over one to two years of follow-up in antidepressant-treated DEPCI patients. The findings suggest that future cognitive enhancer treatment trials for MCI and AD may need to consider including patients with comorbid depression. Separately, we found that adding memantine after open treatment with escitalopram in patients with DEPCI led to a lower rate of conversion to dementia during one year follow-up.

In contrast to the limited, though promising, treatment studies in patients with depression and cognitive impairment, there have been several trials conducted with SSRI and other antidepressants to treat depression in patients with Alzheimer's disease. After an initial report showing no differences between imipramine treatment and placebo, subsequent studies have shown varying response to SSRIs and other antidepressants. A recent study, DIADS, showed no difference between sertraline and placebo.

Our recent meta-analysis showed that the evidence for antidepressant treatment of patients with depression and dementia, although suggestive, does not confirm efficacy. All of the trials were significantly underpowered to detect differences, resulting in inconclusive findings. Variable trial methods, comorbid conditions, and differences in antidepressants employed further confounded findings.

Learning Objectives:
- The participant should understand the diagnostic issues in comorbid depression and cognitive impairment
- The participant should be aware of the treatment trials in comorbid depression and cognitive impairment
- The participant should be able to evaluate the evidence for antidepressant efficacy in patients with dementia and depression
- The participant should understand the pros and cons of using antidepressants in patients with dementia

Literature References:
WHITE MATTER ABNORMALITIES, ACTIVATION OF COGNITIVE AND EMOTIONAL CONTROL NETWORKS, AND LATE-LIFE DEPRESSION

Faith Gunning-Dixon, PhD
Well Cornell Medical College, White Plains, NY

Background: It has been long held that aging-related brain changes contribute to late-life depression. Emotional and cognitive control systems are critical for the modulation of affect, and the processing of conflicting cognitive demands, respectively. Age-related white matter abnormalities in frontolimbic structures may contribute to the development and persistence of late-life depression by impairing the function of these systems.

Methods: We used functional magnetic resonance imaging (fMRI) and T2-weighted MRI imaging in 17 individuals with late-life depression and 17 age-matched comparison subjects to examine whether abnormalities of the emotional and cognitive control systems are mechanisms by which aging-related brain abnormalities contribute to late-life depression. The elderly depressed patients underwent a 2-week, single-blind, placebo lead-in, psychotropic washout phase at the end of which they completed an MRI session. Those who remained depressed then received 12 weeks of escitalopram treatment at the target daily dose of 20 mg.

Results: Relative to comparison subjects, elderly depressed patients exhibited hypoactivation of the dorsal anterior cingulate cortex and the dorsolateral prefrontal cortex in response to a cognitive control paradigm. In contrast, relative to comparison subjects, elderly depressed patients exhibited hyperactivation of emotional control structures, including the subgenual cingulate and the orbitofrontal cortex. These results were influenced by the presence of cerebrovascular disease as measured by white matter hyperintensities (WMH). Further, activation in response to probes of the cognitive and emotional control systems was associated with persistence of depressive symptoms following antidepressant treatment.

Conclusions: Identifying control system abnormalities that both distinguish elderly depressed patients from normal elders and also predict persistence of depression during treatment adds confidence in the role of these abnormalities to the pathophysiology of depression. Further, identifying specific structural and functional impairments of late-life depression can aid the development of clinical instruments and targeted interventions.

Learning Objectives:
- To have knowledge of the brain networks that comprise the cognitive and emotional control systems.
- To understand the depressive symptoms that control system dysfunction can produce.
- To have knowledge of the general pattern of activation abnormalities that are present in late-life depression.

Literature References:

CEREBRAL PERFUSION AND COGNITIVE FUNCTIONING IN LATE LIFE DEPRESSION

R. Scott Mackin, PhD
UCSF, San Francisco, CA

Major depression is associated with tremendous personal suffering, increased risk for medical illness, mortality, and suicide and is the 4th leading contributor to the global burden of disability worldwide. Recent estimates indicate that up to 15% of adults over the age of 65 suffer from Major Depressive Disorder and the economic cost of late life depression (LLD) to society is tremendous. Cognitive impairment represents a significant contributor to disability and increased health care costs in LLD. Executive dysfunction and information processing speed deficits are often considered to be hallmark cognitive features of LLD; however impairments of memory, expressive language, and attention are also frequently reported. Given the heterogeneity of cognitive impairments exhibited by individuals with LLD differentiating the impact of LLD on cognition from the effects of other concurrent conditions, such as neurodegenerative disease, represents a significant challenge. Previous studies have reported strong associations between structural brain abnormalities attributed to cerebrovascular disease and cognitive dysfunction in LLD but the relationship between measures of cerebral blood flow and cortical thickness and cognitive dysfunction in LLD are poorly understood. In this session we will evaluate the relationship between these cortical abnormalities and cognitive functioning in individuals with LLD. Data will be presented from an ongoing study conducted to delineate structural and functional correlates of cognitive dysfunction in LLD.

Learning Objectives:
- To clarify the incidence of specific types of cognitive impairment associated with late life depression.
- To evaluate preliminary data demonstrating patterns of reduced cerebral blood flow and reduced cortical thickness in LLD.
- To evaluate preliminary data suggesting associations between measures of cerebral blood flow and cortical thickness and cognitive functioning in LLD.

Literature References:
REGULATORY PLENARY - NEW FDA AND EMA INITIATIVES IN DEPRESSION AND SCHIZOPHRENIA

Karl Broich, MD, Thomas Laughren, MD, Silvana Borges, MD, Phillip Kronstein, MD

Learning Objectives:

- Have an understanding of the primary EU requirements for drug development programs for Major Depressive Disorder (MDD).
- Have an understanding of the main design issues and outcomes in maintenance trials conducted in drug development programs for MDD over the past 25 years.
- Have an understanding of an FDA initiative to establish data standards for drug development programs targeting schizophrenia.

CLINICAL TRIALS FOR MAJOR DEPRESSION (MDD): CURRENT VIEWS FROM EU

Karl Broich, MD
BfArM, Germany

MDD is one of the most common psychiatric disorders, which is the fourth leading cause of global disease burden. Despite the many treatment options currently approved for MDD, a relevant proportion of patients up to one third does not adequately respond to treatment, even if there is good compliance and the treatment has been taken long enough with an adequate dosage. So there is a clear unmet medical need for patients, in whom even 'state of the art' antidepressant therapy fails to elicit a sufficient treatment response. Following a public consultation period the revision of the 'Note for guidance on Clinical Investigation of Medicinal Products in the Treatment of Depression' gets now finalized. The regulatory requirements for development programs of antidepressant medicinal products are reviewed, special emphasis is given to issues regarding studied patient population (e.g. partial response, treatment resistance) and study designs (short-term and maintenance, active comparator).
PLENARY
8:30 A.M. - 10:00 A.M.

FDA REVIEW OF MAINTENANCE TRIALS FOR MAJOR DEPRESSIVE DISORDER: A 25-YEAR PERSPECTIVE

Silvana Borges MD
Food and Drug Administration, Silver Springs, MD

US Food and Drug Administration (FDA) approves antidepressants for marketing based on short-term clinical trials. The maintenance effectiveness of antidepressants is also of considerable interest. We have compiled efficacy data from a total of 14 antidepressant maintenance trials with a randomized withdrawal design submitted to FDA since the approval of the first second-generation antidepressant in 1987. In these trials, responders to active drug during an open-label phase were randomized to active drug or placebo, and observed for relapse over a period of 6-12 months. Subjects on active drug had significantly lower relapse rates than those on placebo in every study. We will discuss the characteristics of open-label and double-blind phases, relapse rates in drug and placebo arms, and time-course of the treatment effect.

FDA INITIATIVE TO ESTABLISH DATA STANDARDS IN SCHIZOPHRENIA DRUG DEVELOPMENT

Phillip Kronstein, MD
Food & Drug Administration, Silver Springs, MD.

This presentation will give a brief overview of the FDA initiative to develop and implement standards to represent study data submitted in support of regulatory applications, including the latest information and resources for sponsors. Our recent experience in developing data standards specific to schizophrenia drug programs will then be discussed.
PANEL OVERVIEW:
NOVEL METHODS FOR EVALUATING THE HARM-BENEFIT BALANCE IN OUTCOMES OF RANDOMIZED CLINICAL TRIALS: DEMONSTRATION OF A NEW APPROACH

Ellen Frank, PhD, Helena Kraemer, PhD, Meredith Wallace, PhD, Nina Schooller, MD

University of Pittsburgh School of Medicine, Pittsburgh, PA; Stanford University (Emerita), Palo Alto, CA; University of Pittsburgh, Pittsburgh, PA; SUNY Downstate Medical Center

Prior efforts to make use of randomized clinical trials (RCT’s) for clinical decision-making have typically focused on the concept of clinical significance; however, clinical significance, as previously defined (i.e., having a certain level of impact on one of a number of outcome measures) has limited value, especially if it is derived in a traditional statistical fashion. This fact underscores the inherent tension between two key goals of the National Institutes of Health: evidence-based treatment and personalized medicine. Evidence-based treatment typically looks to RCT’s and asks which treatment showed the greater benefit or less harm for the average patient in the study population. In contrast, personalized medicine seeks to understand the factors leading to the individual responses of patients within a population sampled, including both the benefits and the harms. In this symposium we report on the development of a novel methodologic approach to resolving the tension between these two objectives by producing an Integrated Preference Score (IPS) that can be applied to the experience of each patient in a clinical trial and that appears to have special advantages when exploring treatment moderators. This method permits evaluation of the comparative effectiveness of treatments on the basis of the clinical effects of treatments (both benefits and harms) on individual patients rather than on the statistical effects of treatments on individual measures of benefits or harms. In this panel, Dr. Kraemer will describe the rationale and methods for developing this Integrated Preference Score (IPS). Dr. Frank will report on an initial pilot test of this methods based on the results from an RCT entitled, Depression: The Search for Treatment Relevant Phenotypes (MH065376). Dr. Wallace will then describe the results obtained when we used the IPS as the outcome on the basis of which we examined moderation of outcome by clinical variables and by specific biomarkers, effects we had not been able to observe using standard analytic approaches.

Learning Objectives:
- Understand the rationale for simultaneous evaluation of benefits and harms of treatments
- Become familiar with the concept of the Integrated Preference Score (IPS)
- Understand the results obtained in a first pilot demonstration of the IPS method
- Understand the benefits of using the IPS approach in the evaluation of treatment moderators and the development of moderator profiles

RATIONALE FOR AN INTEGRATED HARM-BENEFIT MEASURE

Helena Kraemer, PhD

Stanford University (Emerita), Palo Alto, CA

Background: To find statistically significant effects for psychiatric treatments seems very difficult, requiring very large sample sizes, and even when effects are found, the effect sizes are small. Since power to detect treatment effects depends on recognition of clinically important individual differences in response to the experimental treatment versus the comparator in a randomized clinical trial, a focus on a single primary outcome measure may ignore crucial individual differences. However, using multiple primary outcomes and adjusting for multiple testing both sacrifices power and ignores the impact of joint outcomes on the patient, often producing conflicting conclusions as to which treatment is preferable. The search for moderators of treatment, so important to personalized medicine, is also seriously hampered by this problem.

Proposal: An example is shown to explain and document why ignoring the correlations among clinical benefits and harms, and ignoring their joint effect on patients, can lead to weak and misleading conclusions about the relative effectiveness of two treatments. An integrated preference score (IPS) would consider multiple harms and benefits as they simultaneously affect the patients from the viewpoint of the clinician or consumer. Because the IPS would enhance recognition of individual differences among patients, and recognize the joint impact of harms and benefits on patients, use of an IPS in randomized clinical trials is likely to increase power without increasing sample size, to disattenuate effect sizes, and to encourage identification of moderators of treatment to facilitate personalized medicine. Several options for the development of such an IPS are discussed.

Learning Objectives:
- To consider the impact of clinically important individual differences in finding significant treatment effects in randomized clinical trials.
- To explain why ignoring the simultaneous effect of the multiple benefits and harms that might be related to treatment outcome is crucial both to detecting treatment effects, but also to detecting moderators of treatment.

Literature References:
A PILOT STUDY OF THE INTEGRATED PREFERENCE SCORE (IPS) TO ASSESS HARM-BENEFIT BALANCE IN A DEPRESSION RCT

Ellen Frank, PhD
University of Pittsburgh School of Medicine, Pittsburgh, PA

**Background:** Determining which treatment is to be preferred for an individual patient, given all patient information available, is one aim of personalized medicine. In RCTs in psychiatry, however, there is rarely a single, objective, reliable outcome measure that is sensitive to critical individual differences among patients.

**Method and Results:** We explored the feasibility of quantifying the total clinical value provided by a treatment (including both harms and benefits) in a single metric. First, we asked an expert panel to compare 100 pairs of patients, one from each of two treatment groups in an RCT involving interpersonal psychotherapy (IPT) and escitalopram and to select the patient with the preferred outcome considering both benefits and harms. We derived an integrated preference score (IPS) from these results, such that the differences between any two patients’ IPSs would predict the experts’ preferences. Once the IPS had been computed for all patients in the RCT, a second set of 100 pairs was rated by the panel. Expert preferences were highly correlated with the IPS differences (r=.84). The IPS then was used as the outcome measure comparing IPT and escitalopram. The 95% confidence interval for the effect size comparing treatments indicated clinical true equivalence of the treatments.

**Conclusions:** Construction of a reliable metric that combines benefits and harms of treatments proved quite feasible and could increase the value of RCTs by making clearer which treatments are preferable and for whom. Furthermore, such methods result in more precise estimation of effect sizes, without increasing required sample size.

**Learning Objectives:**
- Achieve familiarity with the methods for developing the integrated preference score (IPS)
- Achieve familiarity with the results of an initial pilot test of the IPS method

**Literature References:**

NOVEL METHODS FOR DEVELOPING AND INTERPRETING MODERATOR PROFILES IN CLINICAL TRIALS

Meredith Lotz Wallace PhD
University of Pittsburgh, Pittsburgh, PA

**Background:** In psychiatric RCTs, there are often subgroups of patients for whom one treatment is preferred over another. Moderation analyses are frequently used in an attempt to identify and describe these subgroups; however, methods to assess the strength or impact of a moderator (or a series of moderators) in a way that is clinically and/or scientifically meaningful are lacking.

**Method and Results:** We applied novel statistical methodology to detect and characterize subgroups of patients for whom FT or SSRI was preferred over the other in a psychiatric RCT. First, we selected a set of independent demographic, clinical, and genetic variables that may moderate treatment outcome. After pairing each IPT patient with each SSRI patient, we regressed each pair’s difference in outcome measure on their average moderator scores and used the resulting coefficients as weights for calculating the optimal combined moderator, M*. We then tested whether M* moderated the effect of treatment on the RCT outcome and used novel effect size methodology confirm that M* had a greater impact than any of the individual moderators. Finally, we used descriptive statistics and pairwise tests to create moderator profiles characterizing the subgroups of patients for whom IPT was preferred over SSRI and vice versa.

**Conclusions:** By using the proposed methodology to develop moderator profiles, we are able to determine much more specifically which treatment is best for which patients than was possible with traditional methods. In this way, the proposed methodology could enable clinicians to use information about individual patients to select or optimize treatment choice and diagnostic testing.

**Learning Objectives:**
- Achieve familiarity with novel methods for developing moderator profiles.
- Achieve familiarity with the results of an application of the proposed methods.

**Literature References:**
PANEL OVERVIEW:
BIOLOGICS FOR ADDICTIONS TREATMENT: VACCINES AND ENZYMES

Thomas Kostén, MD, Phil Skodnick, PhD, Marco Pravetoni, PhD, Kim Janda, PhD, Stephen Brimijoin, PhD

1Baylor, 2NIH, NIDA, 3University of Minnesota, 4The Scripps Research Institute, 5Mayo Clinic

Pharmacotherapies for substance use disorders (SUDs) have traditionally focused on small molecules, but this approach has not yielded approved medications to treat stimulant (e.g., cocaine and methamphetamine) abuse, and provided less than ideal options to treat other SUDs (including nicotine and opioids). However, in contrast to other psychiatric disorders, biological approaches to treat SUDs are emerging as viable alternatives. The basic principle underlying these approaches is to either prevent or markedly slow the rate of entry of the abused substance into the brain. This panel will review state of the art efforts (both preclinical and clinical) to treat SUDs using biological approaches, Paul Pentel/Mario Pravetoni (Univ. Minn.) will review the development of nicotine vaccines, including recent phase 3 clinical studies. Kim Janda (Scripps) will present a novel heroin vaccine that is “immunochemically dynamic” due to its hapten design. This vaccine can prevent both the acquisition of heroin self-administration in naive animals and the reacquisition of self-administration in addicted rats following extinction. Tom Kostén (Baylor) will present genetic and immunological predictors of treatment response in Phase 2 studies of a human cocaine vaccine and describe preclinical studies using cocaine vaccines with improved immunogenicity compared to the vaccine currently in clinical trials. Stephen Brimijoin (Mayo Clinic) will describe the evolution of “engineered” esterases, capable of metabolizing cocaine 1000x more effectively than the wild type enzyme. Recent gene transfer experiments in rats indicate a single such treatment with cocaine hydrolase provides at least six months of protection against resumption of drug-seeking behavior triggered by re-exposure to cocaine.

Learning Objectives:
• To teach clinical providers and researchers about nicotine addiction vaccines status
• To teach clinical providers and researchers about mechanism-based methods to improve drug addiction vaccine efficacy

NICOTINE VACCINE RECENT DEVELOPMENTS

Marco Pravetoni PhD
University of Minnesota, Minneapolis, MN

Vaccination against nicotine shows efficacy in preclinical models for attenuating nicotine behavioral effects, and early clinical trials show increases in smoking cessation rates. A major limitation of nicotine vaccines is their inability to consistently produce high serum antibody levels, and the large individual variability in these levels, which results in many non-responders. Recently, two Phase III clinical trials failed to meet their predetermined endpoints. This suggests that more mechanism-based strategies of improving the efficacy of nicotine vaccines should be studied.

For instance, the efficacy of nicotine vaccines can be enhanced by improvements in hapten and linker design, carrier protein, and adjuvant biology. Pre-clinical studies suggest that polyvalent vaccination strategies involving immunologically distinct nicotine immunogens can produce additive serum antibody levels and might also reduce the individual variability in response, resulting in fewer non-responders. Another approach to improve the efficacy of nicotine vaccines is to combine their use with mechanistically complementary medications. Combining medications with different mechanisms and targets will help to reduce side effects, and will treat different components of nicotine addiction. Exploring novel approaches to increase nicotine vaccine efficacy will be critical to extend their usefulness into clinical settings.

Learning Objectives:
• To teach clinical providers and researchers about nicotine addiction vaccines status
• To teach clinical providers and researchers about mechanism-based methods to improve drug addiction vaccine efficacy

Literature References:
Thursday, May 31, 2012

PANEL
10:30 A.M. - 12:00 P.M.

A VACCINE STRATEGY AGAINST HEROIN
Kim D. Janda, PhD
The Scripps Research Institute, La Jolla, California

Heroin addiction is a wide-reaching problem with a spectrum of damaging social consequences. A vaccine capable of blocking heroin’s effects could provide a long-lasting and sustainable adjunct to heroin addiction therapy. Heroin, however, presents a particularly challenging immunotherapeutic target, as it is quickly metabolized to multiple psychoactive molecules. To create an effective vaccine a singularly chemically dynamic hapten was designed that allows the immune system access to simultaneously sample multiple drug-like antigens, thus an immunodynamic addiction therapeutic tact. We demonstrate the significance of this approach though the extremely rapid generation of robust polyclonal antibody titers with remarkable specificity. Importantly, we will also discuss how both antinociceptive effects of heroin and acquisition of heroin self-administration were blocked in rats vaccinated using this methodology. In addition vaccinated/nonvaccinated animals heroin and associated metabolites serum/brain levels will be discussed.

Learning Objectives:
- The general concept of immunopharmacotherapy to treat addiction
- Vaccines against drugs of abuse can not be generalized as a panacea, thus, each drug and its pharmacodynamic/pharmacokinetic properties must be evaluated on an individual basis
- The strategies behind a dynamic vaccine.

Literature References:
- Animal behavior can be modified using vaccines.

COCAIN VACCINE: GENETIC AND IMMUNOLOGICAL RESPONSE PREDICTORS
Thomas Kosten, MD
Baylor, Bellaire, TX

A human cocaine vaccine has been tested in two placebo controlled randomized clinical trials and found to significantly reduce cocaine use compared to placebo. In these studies we have also investigated predictors of response to this vaccine. About 25% of those vaccinated do not have a sufficient anti-cocaine antibody response to provide effective blockade or relapse prevention from cocaine use. The contributors to this poor antibody response appear to be both immunological and genetic. From the immunological perspective, we and two other research groups have found that up to 20% of cocaine dependent patients already have anti-cocaine antibodies before getting any vaccination. These antibodies are predominantly IgM rather than IgG and have very low affinity for cocaine. Those patients with these baseline antibody levels do not make a robust antibody response to the vaccinations and thereby have a poor treatment response in reducing their cocaine use. The reasons for having these baseline levels of low affinity antibodies are being studied in an animal model. Another interesting predictor of low antibody responses is HLA genotype. This major histocompatibility locus is a predictable driver of immune responses, but the reasons for its involvement in response to a haptenated vaccine are under investigation as we model in animals these variations in hapten immune response.

Learning Objectives:
- To teach researchers and clinical providers about pharmacogenetic predictors of addiction vaccine responses.
- To teach researchers and clinical providers about immunological predictors of addiction vaccine responses.

Literature References:
RODENT STUDIES OF COCAINE HYDROLASE DELIVERED BY GENE TRANSFER AS A POTENTIAL FUTURE TREATMENT FOR REDUCING RELAPSE IN RECOVERING COCAINE USERS

Stephen Brimijoin PhD, Yang Gao, MS
Mayo Clinic, Rochester, MN

We are investigating a gene therapy for cocaine abuse based on an efficient cocaine hydrolase (CocH). The aim is with a single treatment to provide sustained delivery of enzyme at levels capable of destroying typical ‘recreational’ drug doses before they activate reward centers in the brain. Our presentation will review the process by which cocaine hydrolases were developed from human plasma butrylcholinesterase by several research groups using rational structure-based mutation. Data from rat and mouse models will be offered to demonstrate how such an enzyme can be delivered by helper-dependent adenovirus and adeno-associated virus vectors for long-term expression in specific tissues, up to a year or more after a single i.v. injection (Gao and Brimijoin, 2009). We will present findings that support the effectiveness of liver-expressed transgene in reducing certain types of drug-seeking behavior by rats in a dose-escalation model (Carroll et al., 2011). We will show that it is possible to obtain synergistic effects by combining CocH gene transfer with anti-cocaine vaccines (Gao et al., 2010). We will also present unpublished results from rat and mouse experiments indicating that such combinations not only provide protection against the acute lethality but also suppress the chronic liver damage induced by large doses of cocaine (particularly in mice), as indicated by sentinel enzymes in plasma (ALT) and by histopathology. We will conclude with an overview of potential hazards and benefits of systemic gene transfer focused on reducing risk of relapse into drug-seeking after a period of abstinence.

Learning Objectives:
• To teach clinical providers and researchers about gene transfer enzyme treatments for cocaine addiction.
• To understand how antibodies and enzymes differ in regard to their potential for intercepting psychoactive drugs en route to brain

Literature References:
Thursday, May 31, 2012

PANEL
10:30 A.M. - 12:00 P.M.

PANEL OVERVIEW:
FOOD *ADDICTION*: CONCEPTUALIZATION, ASSESSMENT AND APPLICATIONS TO OBESITY

Nicole Avena¹, PhD, Miriam Bocarsly², Gene-Jack Wang³, MD, Eric Stice⁴, PhD,
Caroline Davis⁵, PhD, Mark Gold⁶, MD

¹University of Florida, Gainesville, FL, ²Princeton University, Princeton, NJ,
³Brookhaven National Laboratory, Upton, NY, ⁴Oregon Research Institute,
⁵Eugene, OR, ⁶York University, Toronto, Ontario, Canada

Instances of overeating and obesity are increasing and continue to pose unique challenges for practitioners. Recent research has highlighted overlaps in brain reward systems subserving both overeating and drug addiction, which may contribute to compulsive eating and in some cases obesity. The goal of this panel is to describe relevant research in this area, with presentations on the preclinical and clinical studies of brain reward systems and behaviors related to addiction within the context of palatable food. Ms. Bocarsly (from the Avena Lab) will present research on preclinical models of “food addiction,” focusing on behavioral and neurochemical evidence founded in the mesolimbic dopamine and opioid systems. Dr. Davis will present work showing how characteristics of addiction to food can be assessed in clinical populations using the Yale Food Addiction Scale, and review findings on the incidence of “food addiction” in obese and lean populations, as well as comorbidities with ADHD, depression and binge eating disorder. Dr. Wang will present neuroimaging data, discussing parallels in brain circuitry that are disrupted in both obesity and drug addiction. Finally, Dr. Stice will discuss data predicting unhealthy weight gain and onset of substance use based on fMRI response to receipt, and anticipated receipt, of food and non-food rewards. The panel will be chaired by Dr. Avena, who implements animal models to understand “addiction” to palatable foods. Dr. Gold, who has studied the translational implications and overlaps among obesity, food intake and addiction, will lead the discussion. Collectively, this panel will showcase the new developments in the emerging field of “food addiction” and relate the preclinical and clinical findings to strategies and therapeutic developments aimed at treating obesity and other forms of overeating.

Learning Objectives:
- Describe overlaps in brain reward systems activated in response to both overeating palatable foods and addiction.
- Identify behavioral, neurochemical and brain responses seen in both addiction and overeating, which may relate to obesity and drug use.

BINGE EATING BEHAVIOR IN RATS SHOWS RESULTS IN BEHAVIORAL AND NEUROCHEMICAL CHANGES SUGGESTING DEPENDENCE

Miriam E. Bocarsly¹, Nicole M. Avena², PhD

¹Princeton University, Princeton, NJ, ²University of Florida, Gainesville, FL

Drugs of abuse and palatable foods activate similar neural substrates, suggesting that food can lead to a dependency-like state. To explore this, we have utilized the defining characteristics of drug dependency, and applied them to overeating, using rat models coupled with behavioral and neurochemical techniques. When offered limited daily access to a sucrose solution, rats develop binge-like consumption. When deprived of sugar or given an opioid antagonist, binging rats show signs of withdrawal, as well as craving and sensitivity to drugs of abuse.

Concomitant changes in reward-related brain regions, similar to those seen in drug dependency, are observed in sugar-binging rats. Specifically, changes in dopamine (DA) and acetylcholine (ACh), as well as DA and opioid receptor binding and gene expression, that are consistent with the profile that emerges during drug addiction, are observed. During sugar deprivation, binge eating rats show changes in DA and ACh, similar to that seen during drug withdrawal.

The profile of behavior observed with fat-bingeing is different than that seen in sugar binging, suggesting nutrient specific effects. In particular, animals that binge on fat do not show opioid-like withdrawal. In sum, understanding the relationship between overeating on sugars and fats, through the lens of addiction, may better inform future treatments.

Learning Objectives:
- Identify behaviors associated with addiction that are observed in rat models of overeating.
- Relate the behaviors seen in rats overeating a palatable meal to neurochemical changes.

Literature References:
- Bocarsly ME, Berner LA, Hoebel BG, Avena NM. Rats that binge eat fat-rich food do not show somatic signs or anxiety associated with opiate-like withdrawal: Implications for nutrient-specific food addiction behaviors. Physiol Behav 2011; 104:865-872.
NEUROIMAGING REVEALS OVERLAPS BETWEEN FEEDING AND DRUG ADDICTION IN REWARD-RELATED BRAIN REGIONS

Gene-Jack Wang¹, MD, Nora D. Volkow¹, MD, Panayotis Thanos³, PhD, Joanna S. Fowler³, PhD
¹Brookhaven National Laboratory, Upton, NY. ²National Institute on Drug Abuse, Rockville, MD. ³National Institute on Alcohol Abuse and Alcoholism, Upton, NY

Both drug addiction and obesity can be defined as disorders in which the saliency value of one type of reward (drugs and food, respectively) becomes abnormally enhanced relative to, and at the expense of others. Both drugs and food have powerful reinforcing effects-partly mediated by dopamine increases in the limbic system-that, under certain circumstances or in vulnerable individuals, could overwhelm the brain's homeostatic control mechanisms. Such parallels have generated significant interest in understanding the shared vulnerabilities and trajectories between addiction and obesity. Recent brain imaging studies have started to uncover common features between these two conditions and to delineate some of the overlapping brain circuits whose dysfunctions may explain stereotypic and related behavioral deficits in human subjects. These results suggest that both obese and drug-addicted individuals suffer from impairments in dopaminergic pathways that regulate neuronal systems associated not only with reward sensitivity and incentive motivation, but also with conditioning, impulse control, stress reactivity, and interoceptive awareness. Our imaging findings predominantly derived from positron emission tomography that shed light on the role of brain dopamine in drug addiction and in obesity.

Learning Objectives:
- Describe the brain circuits involved in obesity and drug abuse from neuroimaging studies.
- Recognize the similarity of brain circuits involved in overeating behaviors and drug abuse.

Literature References:

PREDICTING UNHEALTHY WEIGHT GAIN AND ONSET OF SUBSTANCE USE BASED ON FMRI RESPONSE

Eric Stice, PhD
Oregon Research Institute, Eugene, OR

Neural Risk Factors for Unhealthy Weight Gain and Substance Use Onset: A Prospective FMRI Study

Theorists posit that those with hyporesponsive reward circuitry are at increased risk for overeating, whereas others suggest it is hyper-responsivity of this circuitry that confers risk. We conducted a prospective FMRI study with 162 lean teens to test whether aberrant responsivity of reward regions increase risk for initial unhealthy weight gain as well as substance use onset. Youth who showed elevated responsivity of reward regions and blunted activation of inhibitory regions in response to receipt of monetary and food reward were at increased risk for both unhealthy weight gain and substance use onset over a 1-year follow-up, providing support for the reward surfeit theory and inhibitory deficit theory of appetitive behavior, but not the reward deficit model. There was also some specificity, in that elevated responsivity of oral somatosensory regions and the gustatory cortex (which encode fat and sweet tastes respectively), increase risk for weight gain, but not substance use. Data also imply that overeating and substance use result in increased responsivity of reward valuation regions for cues associated with overeating/drug use, supporting for the incentive salience model of appetitive behaviors, but also produce reduced reward region responsivity to food and monetary reward, implying down-regulation of reward circuitry. Collectively, findings suggest strong parallels between initial vulnerability factors for both overeating and substance use, but imply some specificity in risk processes, as well as neural plasticity of reward, attention, and inhibitory circuits that may serve to maintain overeating or substance use.

Learning Objectives:
- Improve knowledge of the neural vulnerability factors for overeating and substance use.
- Learn about plasticity of reward and attention regions that maintain overeating and substance use.

Literature References:
YALE FOOD ADDICTION SCALE AND APPLICABILITY TO OBESITY

Caroline Davis, PhD
York University, Toronto, Ontario, Canada

There is growing evidence of 'food addiction' (FA) in sugar- and fat-bingeing animals. The purpose of the present study was to investigate the legitimacy of this construct in the human condition, and to extend the validation of the Yale Food Addiction Scale (YFAS) - the first tool developed to identify individuals with addictive tendencies towards food. Using a sample (n=90) of overweight and obese adults (aged 25-45 years), and a case-control methodology, we focused our assessments on three domains relevant to the characterization of conventional substance-dependence disorders: clinical co-morbidities, psychogenetic risk factors, and abnormal motivation for the addictive substance. Results were strongly supportive of the FA construct and validation of the YFAS. Those who met the diagnostic criteria for FA - based on the established American Psychiatric Association criteria for substance dependence - had a significantly greater co-morbidity with binge eating disorder, depression, and attention-deficit/hyperactivity disorder compared to their age- and weight-equivalent counterparts. They were also more impulsive, displayed greater emotional reactivity, and reported greater food cravings and 'self-soothing' with food compared to control participants. Finally, using multilocus genetic profiles with 4 functional dopamine polymorphisms, FA were characterized by stronger signaling in the brain's reward pathway, suggesting those with this disorder have a stronger hedonic response to food than their non-FA counterparts. These findings advance the quest to identify clinically relevant subtypes of obesity that may possess different vulnerabilities to environmental risk factors, and thereby could inform more personalized treatment approaches for those who struggle with overeating and weight gain.

Learning Objectives:
- To highlight the importance of identifying subtypes of obesity in order to better inform treatment approaches.
- To draw awareness to the increasing evidence that hyperpalatable foods have the potential for abuse.

Literature References:
PANEL OVERVIEW:
LONG TERM OUTCOME OF CHILDHOOD DISORDERS AND ITS PREDICTORS

Lily Hechtman, MD, Gabrielle Carlson, MD, Golda Ginsburg, PhD, Benedetto Vitiello, MD

1McGill University, 2Stony Brook University School of Medicine, 3The Johns Hopkins University School of Medicine, 4National Institute of Mental Health

Objectives: This panel will focus on the long term outcome of childhood disorders and factors which predict this outcome.

Method: The long term outcome and its predictors will be addressed by Dr. Gabrielle Carlson from Stony Brook University School of Medicine for Bipolar Disorder, Dr. Golda Ginsburg from The Johns Hopkins University School of Medicine for Anxiety Disorder, Dr. Karen Wagner from The University of Texas for Depressive Disorders and Dr. Lily Hechtman from McGill University for Attention Deficit Hyperactivity Disorder. Dr. Ben Vitiello from the NIMH will be the discussant.

Results and Conclusion: The outcome in these childhood disorders is variable and is often influenced by the characteristics of the child, severity of the illness, comorbidity, the family characteristics and functioning as well as treatment.

Conclusion: There may be a need to modify and tailor treatments and follow up to ensure more positive long term outcome.

Learning Objectives:
- Participants will learn about the adolescent and adult outcome of key childhood disorders such as Bipolar Disorder, Anxiety Disorder, Depressive Disorder and ADHD.
- Participants will learn about factors which influence positive and negative outcome in these disorders.

ADOLESCENT AND ADULT OUTCOME IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD) AND ITS PREDICTORS

Lily Hechtman, MD

McGill University, Montreal, Quebec, Canada

Objectives: To describe the adolescent and adult outcome of patients with ADHD and to pinpoint factors which influence these outcomes.

Method: Long term controlled prospective follow up studies will be reviewed and adolescent and adult outcomes in academic, work, social and emotional spheres will be described. Factors such as severity of ADHD symptoms, comorbidity, IQ, socioeconomic status (S.E.S.), family functioning and treatment will be evaluated as to their influence on outcomes.

Results: More than 80% of patients continue to meet criteria for ADHD diagnosis in adolescents. Continuing academic, social and emotional problems are also common. In adulthood, 50-60% of patients continue to have symptoms of the syndrome with continuing work, social and emotional problems. However, close to 30% of patients do fairly well in adulthood while 10% do very poorly. Factors listed above combine to predict outcome.

Conclusions: Long term outcome in adolescents and adults with ADHD can be positive as well as negative. This outcome is influenced by a variety of factors.

Learning Objectives:
- To inform participants about the adolescent and adult outcome in patients with ADHD
- To inform participants about the various factors which influence this outcome

Literature References:
LONG TERM OUTCOME OF BIPOLAR DISORDER
Gabrielle Carlson MD
Stony Brook University School of Medicine, Stony Brook, NY

Objective: To describe the long term outcome of youth with bipolar disorder in community, high risk and clinical samples.

Method: literature review with description of the 10 year course of bipolar disorder in the Suffolk County Mental Health Project

Results: The bipolar controversy in youth is addresses the question of whether children have a classic manic depressive presentation (narrow) or a specific mood dysregulation (broad) phenotype. Rates, comorbidities, and outcome differ depending on which concept is considered.

Conclusion: Broader phenotype has a universally worse prognosis.

Learning Objectives:
- The attendee will be able to describe the long term outcome of bipolar youth in community samples
- The attendee will be able to describe the long term course of bipolar disorder in high risk samples
- The attendee will be able to describe the long term course of bipolar disorder in clinical samples

Literature References:
- Birmaher B, Axelson D, Goldstein B, et al; 4-year longitudinal course of children and adolescents with bipolar.

LONG-TERM OUTCOMES FOR YOUTH WITH ANXIETY DISORDERS
Golda Ginsburg PhD
The Johns Hopkins University School of Medicine, Baltimore, MD

Anxiety disorders in children are considered “gateway” illnesses, as they predict subsequent psychiatric disorders including anxiety, depression, and substance use disorders. From a public health perspective, the question of whether early and effective treatment of anxiety disorders can prevent or reduce the risk of onset of these distal psychopathologies is paramount. The high rates of anxiety disorders and their associated short- and long-term sequelae indicate that excessive fear, worry, and anxiety in children are a significant public health concern. A primary goal of this presentation is to describe the yet unpublished long-term findings from the NIMH-funded multisite Child/Adolescent Anxiety Multimodal Treatment Study (CAMS) and to place these findings in the context of other follow up studies of anxious youth. The presentation will review evidence from CAMS regarding: 1) the durability of the CAMS treatments, 2) predictors of remission and relapse for anxiety disorders, and 3) the relation between effective treatment and other long-term outcomes including psychopathology (e.g., depression, substance use) and functioning (e.g., school, vocational success). These findings will be compared and contrasted with published studies examining the long-term outcomes of youth with anxiety disorders.

Learning Objectives:
- To teach clinical providers and researchers about nicotine addiction vaccines status
- To teach clinical providers and researchers about mechanism-based methods to improve drug addiction vaccine efficacy

Literature References:
LONG TERM OUTCOME OF DEPRESSIVE DISORDERS

Karen Wagner, MD, Gabrielle Carlson, MD

1The University of Texas at Galveston, Galveston, TX, Stony Brook University School of Medicine, Stony Brook, NY

Depression in adolescence is a serious disorder which has an adverse impact on academic, social and family functioning. Response rate to treatment with antidepressant medication is approximately 60% and with combination antidepressant medication and cognitive behavior therapy is approximately 70%. About 50% of adolescents will have a recurrence of an episode of major depression. Depression in adolescence is associated with depression, anxiety, and substance use disorders in adulthood.

Learning Objectives:
- To increase knowledge about treatment response in adolescent depression
- To increase knowledge about mental health outcomes of adolescent depression

Literature References:
WORKSHOP OVERVIEW:
KEEPING IT REAL: QUANTIFYING CLINICAL RELEVANCE IN TREATMENTS FOR PSYCHIATRIC DISORDERS

Leslie Citrome, MD, Jamie Karagianis1 MD, Terence Ketter2 MD, Christoph Correll1 MD, Keming Gao2 MD

1Eli Lilly, Indianapolis, IN, 2Stanford, Stanford, CA, 3Hofstra North Shore LIU School of Medicine, Glen Oaks, NY, 4Case Western Reserve University School of Medicine, Cleveland, OH

Over the years researchers and their students have been tyrannized by P values so that obtaining a P < 0.05 becomes a goal in itself, all too often without taking a step back and asking the question if what is being accomplished is actually clinically important. For the practitioner applying data towards the treatment of an individual patient, assessing clinical relevance is a critical step in medical decision-making. This workshop includes several presentations that expand on this theme, starting with a perspective on the teaching and application of the philosophy and principles of evidence-based care by Jamie Karagianis, MD. Two presentations review clinical relevance regarding the treatments for two different disease states, starting with schizophrenia by Christoph Correll, MD, and followed by bipolar disorder by Terence Ketter, MD. Themes include measurement-based care and the appropriate interpretation of treatment effects and the subsequent individualization of care. Tradeoffs among different outcomes for these perplexing disorders can be understood by quantifying effect sizes using the clinically intuitive metrics of number needed to treat (NNT) and number needed to harm (NNH). The tension between benefit and risk will be further quantified by introducing the newer concept of Likelihood to be Helped or Harmed (LHH). The concluding report summarizes ways of accurately communicating benefits and harms to patients and payors in a review by Keming Gao, MD. It is hoped that this confluence of presentations and discussion about the quantification of clinical relevance will spur additional interest in the application of the philosophy and tools of evidence-based medicine among clinicians, researchers, authors, editors, publishers and students.

Learning Objectives:
- To understand why evidence-based medicine (EBM) is important
- To learn some ways of making EBM interesting to learn
- To become more aware of the common tools and metrics of EBM

Literature References:
- Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. BMJ. 1995;310:452-454.

TEACHING THE PHILOSOPHY, PROCESS, AND TOOLS OF EVIDENCE-BASED MEDICINE

Jamie L. Karagianis, MD

Eli Lilly, Indianapolis, IN

Clinical practice benefits from research to inform good decision-making. Evidence-based medicine (EBM) helps physicians integrate experience and individual expertise with the best evidence. Various philosophical concepts, including “primum non nocere,” are balanced to achieve this. The tools of EBM, such as number needed to treat, are easy to calculate and to use. Other valuable tools include number needed to harm, attributable risk, and likelihood of being helped or harmed. It is also important to distinguish between relative risk and absolute risk to avoid drawing the wrong conclusions. With the right teaching techniques to grab attention and encourage active participation, real examples can be used to impart practical skills that the clinician can employ in translating research findings into something that helps the individual patient.

Learning Objectives:
- To understand why evidence-based medicine (EBM) is important
- To learn some ways of making EBM interesting to learn
- To become more aware of the common tools and metrics of EBM

Literature References:
- Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. BMJ. 1995;310:452-454.
Thursday, May 31, 2012

WORKSHOP
2:30 P.M. - 5:30 P.M.

CLINICAL RELEVANCE IN TREATMENTS FOR ACUTE BIPOLAR DISORDER

Terence A. Ketter, MD, Shefali Srivastava, MD
Stanford University, Stanford, CA

The United States Food and Drug Administration (US FDA) has approved 9 contemporary treatments for acute mania, but only 2 for acute bipolar depression. These agents differ from one another with respect to their efficacy and tolerability profiles, such that certain medications may be ideal for some patients but not others. We compared therapeutic and adverse effects of treatments for acute mania and acute bipolar depression to inform clinical decision-making by using data from large, randomized, double-blind, placebo-controlled acute mania and acute bipolar depression trials, to assess number needed to treat for response (NNR), number needed to harm for sedation/weight gain (NNWH), and likelihood to help or harm (LHH = NNH + NNT) compared to placebo. For acute mania, lithium compared to other US FDA-approved agents yielded substantively less sedation (NNR = 27 versus 5 to 11) yet broadly similar efficacy (NNR = 4 versus 4 to 8) and thus more favorable efficacy/sedation likelihood (LHH = 6.88 versus 0.70 to 1.80). For acute bipolar depression, lamotrigine compared to US FDA-approved treatments yielded substantively less sedation (NNWH = 12 versus 6 to 24) and efficacy (NNR = 12 versus 4 to 6), but still more favorable efficacy/sedation likelihood (LHH = 1.50) than quetiapine (LHH = 1.00) and efficacy/weight gain likelihood (LHH = 2.8) than the olanzapine plus fluoxetine combination (LHH = 1.5). For acute mania, lithium compared to other US FDA-approved agents yielded less sedation yet similar efficacy, indicating utility for patients sensitive to sedation. For acute bipolar depression, lamotrigine compared to US FDA-approved treatments yielded better tolerability but poorer efficacy, suggesting utility in patients sensitive to sedation/weight gain with milder episodes, whereas the US FDA-approved treatments may have utility in patients with more severe episodes.

Learning Objectives:
- Understand comparative therapeutic efficacy benefits for treatments for bipolar disorder
- Appreciate comparative side effects risks for treatments for bipolar disorder
- Compare therapeutic and side effects of treatments for acute bipolar disorder to inform clinical decision-making

Literature References:

CLINICAL RELEVANCE OF TREATMENTS FOR SCHIZOPHRENIA

Christoph Correll, MD, Taishiro Kishimoto1, MD, PhD
1 Hofstra North Shore LIJ School of Medicine, Glen Oaks, NY, 2 The Zucker Hillside Hospital, Glen Oaks, NY

Background: To optimize the management of patients with schizophrenia, quantification of treatment effects is crucial. While in research studies, the use of quantitative assessments is ubiquitous; this is not the case in routine clinical practice, creating an important translational practice gap.

Methods: Summary of methodological aspects in the assessment of therapeutic and adverse antipsychotic effects in schizophrenia, including definitions and methods of measurement based assessments and factors that can interfere with the valid quantification of treatment effects. Proposal of pragmatic and clinically meaningful ways to measure and report treatment outcomes.

Results: While rating scales are ubiquitous in schizophrenia research and provide the evidence base for treatment guidelines, time constraints, lack of familiarity with and/or training in validated assessment tools limits their routine clinical use. Simple, but valid, assessment instruments need to be developed and implemented to bridge this researchpractice gap. Moreover, results from research trials need to be communicated in clinically meaningful ways. This includes the reporting of effect sizes, numbers-needed-to-treat and harm, confidence intervals and absolute risk differences. Some important outcomes, such as treatment response, should be reported in escalating intervals using incrementally more stringent psychopathology improvements. Nevertheless, even with quantification, it remains challenging to weigh individual efficacy and adverse effect outcomes against each other and to decide on the targeted/desired improvement or outcome, while also incorporating that in patient-centered and shared decision making.

Conclusions: Quantification of treatment effects in schizophrenia is relevant for patient management, research, and the evaluation of health care systems. Beyond consensus about meaningful outcome definitions, reporting strategies, pragmatic tool development and implementation, the discovery of novel treatment mechanisms and related biomarkers is hoped to advance measurement based approaches in schizophrenia and thereby improve patient outcomes.

Learning Objectives:
- Summarize opportunities of and barriers to measurement based approaches in psychiatry
- Review definitions and terminologies used to communicate outcomes in schizophrenia
- Become aware of rating tools that are either helpful for research and/or real world clinical use
- Identify areas and settings where increased measurement based approaches can improve patient outcomes

Literature References:
COMMUNICATING BENEFITS AND HARMs TO PATIENTS AND PAYORS

Keming Gaq MD

Case Western Reserve University School of Medicine, Cleveland, OH

Communicating benefits and harms to patients and payors is essential for high quality care. However, there has never been a guideline or consensus on how to communicate benefits and harms to patients and payors. The goal of this presentation is to identify key elements for communication among clinicians, patients, and payors to achieve maximal benefits and minimal harms. Evidence-based medicine, number needed to treat to benefit (NNTB) or harm (NNTH), and the likelihood of being helped or harmed (LHH) have been advocated as the basis for communication in all specialties of medicine. Phase-dependent communication of benefits and harms is novel, especially for patients with different phases of illness such as bipolar disorder. Duration-dependent (short-term versus long term) communication is essential for all psychiatric disorders to reduce the burden of relapse and long-term side effect. For drugs with multiple therapeutic indications, a disease-dependent approach is critical to maximize benefits and minimize harms. Exclusion of comorbid psychiatric disorders in pivotal efficacy trials has affected their generalizability. Communicating cost (direct versus indirect cost) is inevitable and a key component for reducing health care expenditures. However, the results of current cost-effectiveness analyses have been inconsistent and even contradictory.

Learning Objectives:
- To learn key elements for communication among clinicians, patients, and payors
- To understand the importance of using number needed to treat to benefit, number needed to treat to harm, and likelihood of being helped or harmed for decision-making

Literature References:

CIRCLING BACK: WHAT DO PATIENTS REALLY CARE ABOUT?

Leslie Citrome, MD

Leslie Citrome, MD, MPH, Suffern, NY

Attention to a patient’s values and preferences is an essential component to the practice of evidence-based medicine. Some goals such as “recovery” are difficult to quantify, but other aspects of care are more easily measured, such as achieving a certain threshold of symptom reduction and the avoidance of specific adverse effects when prescribing medications. The example of Major Depressive Disorder (MDD) will be used to illustrate these ideas. In striving for remission the clinician is also required to manage the occurrence of adverse effects. The most objectionable adverse effect is in the eye of the beholder—what is very disconcerting to one patient, and leads to non-adherence, may be viewed as benign by another. The clinician may also have different perceptions from the patient regarding the importance of the adverse event in terms of long-term consequences—an example of this would be weight gain. The US Food and Drug Administration has approved three different second-generation antipsychotics as adjunctive agents for the management of MDD. Having 3 choices, each with different profiles regarding akathisia, weight gain, and somnolence is helpful. The incidence of these adverse effects can be used to calculate Number Needed to Harm and can be contrasted with the Number Needed to Treat to achieve response or remission.

Learning Objectives:
- To understand the importance of a patient’s values and preferences
- To understand the heterogeneity among patients regarding the perception of adverse effects
- To understand some of the advantages and limitations in calculating Number Needed to Harm

Literature References:
WORKSHOP OVERVIEW:
STRATEGIES FOR INCOMPLETE DATA IN RANDOMIZED CLINICAL TRIALS

David Sheehan¹, MD, Craig Mallinckrodt², PhD, Geert Molenberghs², PhD,
Richard Entsuah³, PhD, MS

¹University of South Florida College of Medicine, Eli Lilly and Company, Hasselt
University and Katholieke Universiteit Leuven, ²Merck Research Laboratories

Missing data are ubiquitous in clinical trials in psychiatry. This phenomenon introduces bias in the estimate of the treatment effect. It also reduces statistical power, precision, generalizability and trial feasibility. The National Research Council convened a panel on Handling Missing Data in Clinical Trials in 2009 with support from the US Food and Drug Administration. The panel's recommendations were published in 2010. Here we consider their three general areas of focus: prevention, analysis of incomplete data, and sensitivity analyses.

There is no substitute for complete data. Therefore, the field must make a greater effort at prevention of missing data. A variety of methods of analyzing incomplete data are used in psychopharmacology. Some of these are appropriate; others are misleading, at best. Finally, there is no convention for the application and interpretation of sensitivity analyses. In this session, speakers will bring industry, academic, and regulatory perspectives on strategies for prevention of missing data, analysis of incomplete data, and sensitivity analyses. Methods will be described and discussed emphasizing examples from psychiatric clinical trials.

Learning Objectives:
- To learn methods to prevent missing data
- To learn strategies for analyzing incomplete data
- To learn strategies for sensitivity analyses

CLINICALLY PRACTICAL WAYS OF HANDLING INCOMPLETE DATA:
EXPERIENCE FROM THE CLINICAL RESEARCH TRENCHES

David V. Sheehan, MD
University of South Florida College of Medicine, Lutz, Florida

There are 2 major ways of handling the mess associated with incomplete data in clinical trials. The most common and well-studied method is to use a statistical adjustment e.g. data imputation to compensate for the missing data. My co-presenters will discuss this approach. The other, rarely implemented and less studied approach is to avoid the practices that allow the problem to occur in the first place. I will review this problem and its solution.

The biggest problem is the persistent use of paper and pen to capture research data at the time of the visit. This method results in substantial missing data (omission) and double entries and ineligible input (commission). Errors of omission or commission on even one item on a 25 item scale affects not only the scoring of that item, but also affects the total and factor scoring for the entire scale for that visit. Another issue is the rate of inconsistency between the scores on different items and on different scales during the same visit, resulting in further loss of valuable data. Power analysis estimates of the sample size needed to get statistical significance underestimate the amount of data lost from these errors of omission and commission. Most of these problems could be avoided by using intelligently designed computerized direct data capture systems at the time of the visit and by ending the use of paper as the first place the data is recorded. Other ways of reducing data loss through improving visit attendance and reducing drop-outs will be discussed.

Learning Objectives:
- Appreciate the extent to which incomplete data problems can be avoided at the data capture level and the impact of failure to do so has on the outcome of clinical studies in CNS.
- Appreciate the practical methods that can be used to minimize missing or incomplete data by clinical researchers during the conduct of the study.

Literature References:
- Entsuah R. Etran: a ranking procedure for handling missing data.
SENSIBLE APPROACHES FOR ANALYSES OF INCOMPLETE CLINICAL TRIAL DATA

Craig H. Mallinckrodt PhD
Eli Lilly, Indianapolis, IN

This presentation will focus on a case study from a clinical trial in depression to illustrate the NRC Panel’s recommendations for handling missing data from continuous endpoints. Specifically, the robustness of the a priori specified likelihood-based (MMRM) primary analysis will be assessed using a variety of MNAR analyses and an inclusive modeling multiple imputation approach, along with influence and residual diagnostics for the primary analysis. A novel method of imputing missing data for both the drug and placebo groups from the placebo group will be presented both as a likely conservative MNAR analysis and as an alternative to BOCF to assess effectiveness.

Learning Objectives:
- Understand new guidance
- Illustrate implementation of new guidance

Literature References:

ANALYSIS AND SENSITIVITY ANALYSIS FOR INCOMPLETE DATA FROM CLINICAL STUDIES

Geert Molenberghs, PhD
Hasselt University and Katholieke Universiteit Leuven, Diepenbeek, Belgium

Over the last couple of decades a variety of models to analyze incomplete multivariate and longitudinal data have been proposed, many of which allowing for the missingness to be not at random (MNAR), in the sense that the unobserved measurements influence the process governing missingness, in addition to influences coming from observed measurements and/or covariates. The fundamental problems implied by such models, to which we refer as sensitivity to unverifiable modeling assumptions, has, in turn, sparked off various strands of research in what is now termed sensitivity analysis. The nature of sensitivity originates from the fact that an MNAR model is not fully verifiable from the data, rendering the empirical distinction between MNAR and random missingness (MAR), where only covariates and observed outcomes influence missingness, hard or even impossible, unless one is prepared to accept the posited MNAR model in an unquestioning way. We show that the empirical distinction between MAR and MNAR is not possible, in the sense that each MNAR model fit to a set of observed data can be reproduced exactly by an MAR counterpart. Of course, such a pair of models will produce different predictions of the unobserved outcomes, given the observed ones. Theoretical considerations are supplemented with practical illustrations.

Learning Objectives:
- General awareness of fundamental non-identifiability issues with in-complete data
- Perspective on analysis strategies that can be used

Literature References:
APPLICATION OF ETRANK AND OTHER NON-PARAMETRIC METHODS TO HANDLING MISSING DATA ANALYSIS WHEN PARAMETRIC ASSUMPTIONS FAIL

Richard Entsiah, PhD, MS
Merck Research Laboratories, North Wales, PA

Missing data research has gained lots of attention and progress over the last two decades. The concentration has centered around incomplete multivariate and longitudinal data where the missing data pattern is either Missing at Random (MAR) or Missing Not at Random (MNAR). This session of the workshop will discuss when parametric assumptions break down and analysis based on ranks are adopted in particular the ETRANK methods. This approach will be compared to other rank methods and a parametric method - the constraint Longitudinal Data Analysis (cLDA) method.

Learning Objectives:
- At the end of this workshop participants would have learnt about efficient methods of dealing with missing data when basic parametric assumptions are violated.
- These methods could be adopted as primary analyses method not only as sensitivity analysis for continuous longitudinal outcome measures.

Literature References:
WORKSHOP OVERVIEW:
The ALCOHOL CLINICAL TRIALS INITIATIVE (ACTIVE): PROGRESS AND FUTURE DIRECTIONS

Raymond Anton, MD, Raye Litten, PhD, Henry Kranzler, MD, Stephanie O'Malley, PhD

'SMedical University of SC, Charleston, SC,'National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, 'University of Pennsylvania Perelman School of Medicine, Philadelphia, PA,' Yale University School of Medicine, New Haven, CT

The Alcohol Clinical Trials Initiative (ACTIVE) is a consortium of academia, industry, and federal departments (FDA, NIAAA, NIDA) with European industry and regulatory (EMA) representation. Its mission is to provide consensus opinion on the most appropriate and efficient methods for clinical trials in alcohol dependence. Using a data-based approach, the workgroup is exploring a list of salient questions to maximize statistical power, efficiency, and clinical validity in these clinical trials. This workshop will present the progress made by presenting data in a number of crucial areas. Audience questions and feedback will assist in future directions of ACTIVE as it attempts to build a consensus in this area.

Dr. Anton (Chair of ACTIVE) will introduce its mission and progress to date. A high rate of missing drinking data might impact efficiency in alcohol trials. Dr. Kranzler will present data from the COMBINE Study, a multi-center alcohol trial for which more than 90% of drinking data were available, to back test/simulate the effects of missing drinking data on the effect size of naltrexone treatment. Dr. O'Malley will address placebo treatment response in alcohol trials taking into account whether baseline abstinence vs. “lead-in” drinking affects placebo-response. Where possible, the effect of patient characteristics on placebo response will be considered. Dr. Falk will present Cumulative Response Analysis (CRA), a new way of presenting and analyzing drinking outcome data for alcohol clinical trials. Dr. Anton will discuss the use of objective drinking biomarkers (e.g. blood tests) as outcome measures and will present data from the COMBINE Study to illustrate their utility alone, or in combination with drinking data. Dr. Litten will summarize and discuss future directions.

Learning Objectives:
• Learn about the effects of missing data on studies of medication to treat alcohol dependence.
• Learn about the methods available to impute missing data.

Literature References:

THE IMPACT AND MANAGEMENT OF MISSING DATA IN AN ALCOHOL PHARMACOTHERAPY TRIAL

Henry Kranzler, MD, Robert Stout, PhD

'SUniversity of Pennsylvania Perelman School of Medicine, Philadelphia, PA,' Decision Sciences Institute/PIRE, Pawtucket, RI

Missing data can limit the internal validity of treatment trials by reducing statistical power and biasing treatment effects. This is of particular concern in studies of alcohol dependence because missing data are more likely in subjects who relapse to heavy drinking. Despite the best efforts to minimize the amount of missing data, some are inevitable, so methods are needed to account for those data. Although a variety of methods are available to impute missing data, no consensus exists on which is optimal. We used drinking data from the COMBINE study, a 16-week, randomized controlled trial in 1,383 recently alcohol-abstinent subjects to evaluate the effect of and to compare methods for data imputation. Substantial follow-up efforts in the COMBINE study resulted in a within-treatment data set that is 94% complete. We first compared complete data from subjects who discontinued medication treatment prematurely with those who completed treatment. We then examined the effects on statistical power and treatment outcomes of applying a variety of imputation methods. These findings could help to guide the development of medications to treat alcohol dependence.

Learning Objectives:
• Learn about the effects of missing data on studies of medication to treat alcohol dependence.
• Learn about the methods available to impute missing data.

Literature References:
HOW LARGE IS THE PLACEBO RESPONSE IN ALCOHOL CLINICAL TRIALS: EFFECT OF BASELINE DRINKING AND PATIENT CHARACTERISTICS

Stephanie S. O’Malley, PhD
Yale University School of Medicine, New Haven, CT

The response rate to placebo medication can be influenced by a number of factors including trial design and patient characteristics. Ultimately, this response rate has important implications for study design, including the sample size needed to detect an effect. In this presentation, we will examine how study design features, such as requiring pretreatment abstinence and the behavioral platform, influence the response to alcoholism treatment in placebo treated patients using existing data sets, such as the COMBINE study and other trials. We will also examine other patient characteristics, such as duration of pretreatment abstinence, prior treatment exposure, gender and other clinical characteristics as predictors of response to placebo. These findings could be used to guide the selection of patients and sample size estimation for future medication trials for alcohol dependence.

Learning Objectives:
- To understand the contribution of pretreatment abstinence to response rates to placebo.
- To identify other patient characteristics which influence the response to placebo.

Literature References:

USING CUMULATIVE PROPORTION OF RESPONDERS ANALYSIS (CPRA) TO ASSESS TREATMENT OUTCOME IN ALCOHOL CLINICAL TRIALS

Raye Z. Litten, PhD, Daniel Falk, PhD
National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD

Background: A number of “responder” outcomes have been proposed for use in alcohol clinical trials (e.g., abstinence and no heavy drinking). However, these outcomes allow only one definition of successful response. The cumulative proportion of responder analysis (CPRA) includes all of the possible response cutoff points, providing a complete picture of the therapeutic effects of an experimental treatment. CPRA has been used to test the efficacy of analgesics but has not been used to test medications for alcoholism treatment. We evaluated the use of CPRA in two large alcohol treatment trials that examined different medications.

Methods: Data from two alcohol treatment trials, COMBINE and a multi-site topiramate trial, were used to examine the efficacy of naltrexone and topiramate, respectively. We used CPRA to analyze continuous measures of intake drinking—drinking days, heavy drinking days, and drinks per day— as well as reductions in these measures from baseline. All possible cutoff points were evaluated for each measure. Regions of significance, including maximal treatment effects (based on Cohen’s h), were graphed to compare the effects of both medications with a placebo.

Results: Maximal treatment effects were in the “small” range for naltrexone (h=0.29–0.34) and in “medium” range for topiramate (h=0.43–0.69). Treatment group responder curves were not parallel across the entire range of cutoff points, but rather, separated significantly only in the region of the graphs reflecting lower levels of drinking. In general, effect size increases of 0.10–0.15 were observed going from the lowest drinking level cutoff (e.g., abstinence and no heavy drinking) to the cutoff associated with the maximal treatment effect. Imputing missing data did not affect results in the COMBINE trial but did affect the topiramate trial.

Conclusion: CPRA shows the medication response over a full range of cutoff points, providing a more comprehensive view of the efficacy profile of a treatment. In addition, it permits ready identification of the cutoff point associated with the maximal treatment effect—information that is especially useful in the context of its clinical utility. Future studies should investigate the health-related consequences and economic costs associated with various CPRA cutoff points.

Learning Objectives:
- To become familiar with the CPRA methodology and how it can be used to present clinical trial data.
- To understand how treatment effects observed in alcohol clinical trials vary according to the definition of a treatment responder.

Literature References:
ALCOHOL BIOMARKERS AS OUTCOME MEASURES ALONE OR IN CONJUNCTION WITH DRINKING AS OUTCOMES IN ALCOHOL CLINICAL TRIALS

Raymond F. Anton, MD
Medical University of South Carolina, Charleston, SC

The Alcohol Clinical Trials Initiative (ACTIVE) is a consortium of academia, industry, and federal departments (FDA, NIAAA, NIDA) with European industry and regulatory (EMA) representation. Its mission is to provide consensus opinion on the most appropriate and efficient methods for clinical trials in alcohol dependence. Using a data-based approach, the workgroup is exploring a list of salient questions to maximize statistical power, efficiency, and clinical validity in these clinical trials. This workshop will present the progress made by presenting data in a number of crucial areas. Audience questions and feedback will assist in future directions of ACTIVE as it attempts to build a consensus in this area.

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Learning Objectives:
- To better understand the challenges and opportunities in performing clinical trials for alcohol dependence.
- To appreciate new outcome measures, missing data, and placebo response in alcohol trials.

Literature References:
WORKSHOP OVERVIEW:
DEALING WITH CROSS CULTURAL DIFFERENCES IN STANDARD RATING SCALES IN PSYCHIATRIC RESEARCH
Lawrence Yang¹, PhD, Carla M. Canuso, MD, PhD, Richard Keefe², PhD, David Sheehan², MD
¹Columbia University, New York, NY; ²Janssen Janssen Research and Development, Titusville, NJ; ³Duke University, Durham, NC; ⁴University of South Florida College of Medicine Tampa, FL

Purpose: This workshop plans to explore cross-cultural differences in response styles when using psychiatric rating scales. Differences in reliability may be due to cultural backgrounds, language, or interpretation of responses. In clinical trials, good interrater reliability across sites is central to reducing error and achieving statistical power. In non-psychotic psychiatric illnesses, cultural background shows a substantial influence on the interpretation of behavior as either normal or pathological (Hambleton, 2005). Studies using rating scales should not be undertaken in the absence of prior knowledge about cross-cultural differences, and the results of these scales may not adequately assess cultural disparities (Myers, 2011). It is important to consider the degree to which differences in ratings are the result of differences in response styles or if they reflect true cultural differences. An understanding of the extent and nature of differences in the use of rating scales has theoretical as well as methodological implications for clinical trial design and outcomes.

Methodology/Results: Studies have identified cultural differences among rating scales (WHO Quality of Life Inventory for depression; our own Rasch analysis of the PANSS). Rasch analysis has shown that, to a greater or lesser degree, respondents of different cultures rate high or low for specific items and some items show poor reliability across cultures.

Importance: When investigators pool data from different countries, items showing differences among cultures affect interpretation of treatment outcomes. Rating scale training should focus on cultural differences, and data monitors should develop ways to adjust rating scale responses, so that a particular response value means the same regardless of country of origin.

Learning Objectives:
• To present the extent to which cross-cultural differences exists within rating scales in schizophrenia and depression trials
• To examine cultural differences in response styles and assess the magnitude of distorting effects. To present sophisticated approaches that is global to deal with cultural differences in scale usage

Valuation Methods and Implementation Considerations for International Use of Cognitive and Functional Outcomes
Richard Keefe, PhD
Duke University, Durham, NC

The increase in the number of CNS trials outside of North America and Western Europe has required the use of a variety of key outcome measures away from the cultures in which they were developed. Culture is a major determinant of the manner by which psychopathology, including cognitive and functional impairment, is experienced, reported, and assessed. Therefore, regional and country-specific patterns of measuring psychopathology, cognition, and functional outcomes are potential confounds in interpretation of clinical trials data. Guidelines for adapting psychological tests for different languages and cultures have been established and refined for several decades. The International Test Commission (ITC) published guidelines for international test adaptation in 2001 focusing on the necessity of establishing construct, functional, translational and metric equivalence to use a test across cultures. However, these considerations are often not implemented in clinical trials in international settings. This presentation will address the processes for validating and standardizing administration procedures for performance-based outcomes and the current status of validation and standardization of key cognitive and functional outcomes such as the MATRICS Consensus Cognitive Battery (MCCB), Brief Assessment of Cognition in Schizophrenia (BACS), and the UCSD Performance-based Skills Assessment. The presentation will include data from large international trials suggesting that the test-retest reliability of these key instruments may vary across countries. In addition, the errors made by testers differ considerably across countries, suggesting that additional surveillance procedures may facilitate the reliability and validity of data collected in some international trials.

Learning Objectives:
• To understand the impact of culture on cognitive and functional outcome assessment
• To learn the processes for establishing reliable and valid instruments in international clinical trial settings

Literature References:
CROSS-CULTURAL DIFFERENCES IN THE DIAGNOSIS AND ASSESSMENT OF SCHIZOAFFECTIVE DISORDER

Carla M. Caruso, MD

Janssen Research and Development, Titusville, NJ

Background: Schizoaffective disorder, characterized by symptoms of both schizophrenia and a mood disorder, is defined differently by DSM-IV and ICD-10. Results from a recently completed feasibility study, rater-certification, and a phase III registration program, conducted in 4 globally diverse regions (Asia Pacific, Eastern Europe, India, and the US), provide data to explore region-specific differences in diagnosis and assessment of schizoaffective disorder.

Methods: 1) An initial feasibility study evaluated the frequency of schizoaffective disorder using the Mini-International Neuropsychiatric Interview (MINI) in 208 adult patients experiencing psychotic symptoms. Charts of participating subjects were reviewed for clinical diagnosis and medication use. 2) Rater training was provided to investigators participating in one of the two pivotal trials. Kappa values were calculated relative to expert rating for the 30-item PANSS questionnaire across all raters and for all raters within a country. 3) Pooled data (n=627) from two international, 6-week double-blind, placebo-controlled clinical studies of an atypical antipsychotic in adults with acute of schizoaffective disorder. Change in PANSS total score from baseline to endpoint was evaluated by region (EU vs non-EU), as was change in YMRS and HAM-D 21 score among subjects with prominent baseline manic and depressive symptoms, respectively.

Results: 1) The frequency of schizoaffective disorder varied by region, ranging from 23.3%-40.8% using the MINI and 11.9%-24.5% by clinical diagnosis. 2) Kappa values in Study 1 ranged from 0.799 for the United States to 0.853 for Russia; Kappa values in Study 2 ranged from 0.734 for Korea to 0.843 for Bulgaria. 3) Treatment effect sizes were similar across regions for the PANSS, YMRS and HAM-D.

Conclusion: Despite the complexity of diagnosis and differences in diagnostic criteria, schizoaffective disorder can be diagnosed and consistently assessed across globally diverse regions.

Learning Objectives:
- To understand differences in the frequency of schizoaffective disorder in 4 globally diverse regions.
- To understand similarities and differences in PANSS ratings across these regions

Literature References:

PRELIMINARY FINDINGS OF CROSS-CULTURAL DIFFERENCES WITH THE POSITIVE AND NEGATIVE SYNDROME SCALE (ACROSS 6 GEOGRAPHICAL REGIONS) USING RASCH ANALYSIS

Lawrence Yang, PhD

Columbia University, New York, NY

Background: The study examined the cross-cultural differences in PANSS items across six geographic regions using training data. We examine how each item function across regions, to enhance the measurement properties by providing additional training for raters on items deemed problematic for that region.

Methods: There were 1179 raters from six geographic regions, Maritime Asia (n=202), India (n=185), Northern Europe (n=126), Russia-Europe (n=197), Southern Europe (n=162), USA (n=297). Rasch model was used to identify invariance of item calibrations. Lower item calibration reflects items with less difficulty scoring; higher item calibration reflects items with more difficulty scoring.

Results: Positive Subscale P3.Hallucinatory Behavior was the easiest to score for all regions ranging from Russia (Δ=0.82) to Asia (Δ=0.63), followed by P6.Suspiciousness/Persecution (USA (Δ=0.93) to Northern Europe (Δ=0.58)). All regions found P5.Excitement the most difficult to score. Negative Subscale: The most difficult item to score for all regions is N7.Stereotyped Thinking with India showing the most difficulty Δ=0.69, and Northern Europe and USA showing the least difficulty Δ=0.21. N1.Blunted Affect was also difficult to score for most countries, Southern Europe (Δ=0.30), Asia (Δ=0.28), Russia-Europe (Δ=0.22) and India (Δ=0.10). General Psychopathology: The most difficult item to score for all regions is G4.Tension. Raters from Asia had difficulties scoring item G5. Manners and Posturing. Δ=.81.

Conclusions: Using a unique Rasch analysis we identified significant differences for numerous PANSS items, possibly caused by a lack of equivalence of translated versions, cultural differences among item interpretations, or scoring parameters. Knowing which items are problematic for various cultures can guide PANSS training for geographic regions.

Keywords: Schizophrenia, PANSS

Conflicts of Interests: No authors have conflicts of interest related to this study to disclose.

Learning Objectives:
- To examine the differences for items of the PANSS across 6 geographic regions
- To review possible training and data monitoring procedures to avoid cross cultural differences for PANSS items

Literature References:
Psychiatric research is now a global enterprise. A clinical trial using the same protocol to investigate a new compound for regulatory approval is typically conducted in 20 to 60 sites in many different countries concurrently. The structured diagnostic interviews and scales used in these trials must be harmonized to achieve consistency across all the participating languages and cultures. There is a tension between achieving consistent linguistic meaning across the languages and in being culturally sensitive. Speaking too directly, though very clearly in one language, may be perceived as rude or offensive in another language. Speaking in very flowery language and in never ending sentences may be perceived as very erudite in one language, but appear confusing, unclear and foolish in another. Punctuation, capitalization of letters, word sounds and color, word symbols and languages using multi-byte character sets or a combination of these, present challenges in the search for linguistic and cross cultural harmonization. Slang words in common usage and easily understood in one language may be difficult to translate into another. Some languages have no words for anxiety or depression or use the same word for both states, yet may have popular words for words rarely used in English, like anhedonia. Some languages have many words for depression, while English has essentially one. Some cultures interpret certain symptoms or signs as evil or desirable and therefore wish to deny, minimize or exaggerate their presence. This minimization or exaggeration can be further magnified by the way in which the symptom is elicited. Children's use of language in each culture further complicates all of the above.

Faced with all these challenges, the scientific community has evolved a system for harmonizing the language and cultural differences. Few clinical researchers know much about these “solutions,” nor in this complex, sophisticated and very time-consuming methodology, nor in how it is implemented. This methodology, with its strengths and limitations, will be described in detail, using a multimedia presentation.

**Learning Objectives:**

- Appreciate the extent to which linguistic and cultural differences in the understanding, interpretation and use of depression and anxiety rating scales can influence results in international research studies
- Appreciate the methodology that has evolved in the translation of scales and structured interviews to harmonize the cultural and linguistic differences and problems across languages and cultures

**Literature References:**

PANEL
8:30 A.M. - 10:00 A.M.

PANEL OVERVIEW:
REAPING THE BENEFITS OF DATA POOLING AND SHARING TO ADDRESS QUESTIONS IN DESIGNING RCT’S AND PREDICTING OUTCOMES OF ANTIPSYCHOTIC AND ANTIDEPRESSANT DRUGS

Jonathan Rabinowitz PhD, Rudolf Uher MD, MD, Ni Khin MD, MD, Bruce Kinori MD

1Bar Ilan University, Raanana, Israel; 2King’s College London, England; 3FDA, Silver Spring, MD, 4Eli Lilly and Company, Indianapolis, IN

The purpose of this panel is to present data from three large data pooling efforts that are not available through traditional clinical trial design or meta-analysis, with implications for improved trial design and personalizing treatments. Data are from (1) FDA pooled placebo controlled RCT’s of antidepressants (n=21,611, 81 trials) and antipsychotics (n=12,585, 33 trials); (2) NewMed’s repository of antipsychotic RCT data from placebo controlled (n=9171, 29 trials) and active controlled (n=12,846, 30 trials) trials conducted by AstraZeneca, Janssen, Eli Lilly, Lundbeck, and Pfizer; and (3) NewMed’s repository of genetic and outcome data from placebo controlled antidepressant trials conducted Pfizer, GSK and Roche (n=1790, 5 trials) - the largest pharmacogenetic antidepressant sample in existence.

Findings to be presented: (1) Role of genetic variants in predicting response to commonly used antidepressants; (2) Effect of benzodiazepine use on placebo and active treatment response; (3) Comparison of statistical power attainable using LOCF and mixed models and a composite test of completion and symptom change among completers; (4) Role of demographic and illness history variables in predicting treatment response; (5) Regional differences in treatment response; (6) Effect of proportion of patients on placebo and active treatment on outcomes; (7) Placebo vs. active treatment differences discernible over the course of the trial; (8) Change in placebo response over the last decades; (9) Differences in outcomes between fixed vs. flexible dose studies.

Learning Objectives:
- Participants will learn about the benefits of data sharing.
- Participants will learn about ways to improve efficiency of clinical trials.

IMPROVING EFFICIENCY OF RCT’S OF ANTIPSYCHOTIC TRIALS: LESSONS LEARNED FROM THE NEWMEDS REPOSITORY OF RCT DATA FROM ASTRAZENeca, JANSSen, ELI LILLY, LUNDBECK, AND PFIZER

Jonathan Rabinowitz PhD
Bar Ilan University, Raanana, Israel

There is interest in improving the design of RCTs to more efficiently demonstrate treatment response in schizophrenia (1). NEWMeds repository includes anonymized patient data from AstraZeneca, Janssen, Eli Lilly, Lundbeck, and Pfizer from 29 placebo-controlled trials of second-generation antipsychotics (n=9171) and 30 active controlled trials (n=12,846).

Results: (a) Benzodiazepine use was not associated with significantly greater placebo or active treatment response suggesting that its use does not confound study results: (b) Statistical power can be increased over standard methods in active treatment comparison studies by using a composite test of completion and symptom change (2); (c) Females and persons age 30 or under with at least 4 years since onset showed increased antipsychotic response; (d) US sites have less placebo vs. active treatment difference than Eastern European sites; (e) Proportion of patients on placebo and active treatment does not have a marked effect on trial results; (f) Possible evidence of increase in placebo response over the last decades; (g) Differences in outcomes between fixed vs. flexible dose studies; (h) Trial results can be known earlier and trials can probably be made shorter.

Learning Objectives:
- Participants will learn how trial design features such as inclusion criteria, region and duration can affect study results.
- Participants will learn a statistical method that can increase power in active controlled studies without imputing data.

Literature References:
CAN GENOME-WIDE PHARMACOGENETICS HELP PREDICT RESPONSE OF ANTIDEPRESSANT TREATMENT FOR MAJOR DEPRESSIVE DISORDER: NEWMEDS CONSORTIUM OF ACADEMIC AND INDUSTRY-LED STUDIES

Rudolf Uher, MD, Katherine E. Tansey, PhD
King's College London, London, England, United Kingdom

It has been suggested that outcomes of antidepressant treatment for major depressive disorder (MDD) could be significantly improved if treatment choice is informed by genetic data. To test the hypothesis that a single common genetic variant exists that could predict response to antidepressants in a clinically meaningful way, the NEWMEDS consortium, an academia-industry partnership, assembled a database of over two thousand individuals with MDD, prospectively measured treatment outcomes with serotonin reuptake inhibiting (SRI) or noradrenaline reuptake inhibiting (NRI) antidepressants and available genetic samples from five studies. The resulting dataset of 1790 individuals with high-quality genome-wide genotyping provided adequate power to test the hypotheses that antidepressant response or a clinically significant differential response to the two classes of antidepressants could be predicted from a single common genetic polymorphism. In spite of adequate power, none of the more than half million genetic markers significantly predicted response to antidepressants overall, SRI, NRI or differential response to the two types of antidepressants. The negative finding from the largest pharmacogenetic study carried out to date suggests that no single common genetic polymorphism could help personalize the treatment of depression in a clinically meaningful manner.

Learning Objectives:
- Realistically evaluate the role of pharmacogenetics in personalizing antidepressant treatment
- Appreciate the potential of transparent collaboration between academia and industry

Literature References:

FINDINGS ON PLACEBO RESPONSE AND TREATMENT EFFECT FROM POOLED ANALYSIS OF ANTIPSYCHOTIC AND ANTIDEPRESSANT DRUGS SUBMITTED TO THE FDA

Ni A. Khin, MD
FDA, Silver Spring, MD

Purpose: There has been concern about a rising placebo response and a declining treatment effect in psychiatric trials as well as the implications of increasing conduct of such trials outside the US. Exploratory analyses were conducted to examine differences in efficacy data pooled from randomized placebo-controlled trials submitted in support of new drug applications for the treatment of schizophrenia (32 trials) and major depressive disorder(MDD) (81 trials) over the last two decades.

Results: An increasing placebo response and a diminishing treatment effect over time were observed in North American (NA) trials (~11 to -6 PANSS in schizophrenia; -3 to -1.8 HAMD in MDD). The overall trial success rate over the two decades was also declining slightly despite increasing sample sizes in recent trials (~85% vs. 74% in schizophrenia; 55% vs. 50% in MDD). Trials with higher mean baseline scores tended to show larger treatment effects than those with lower scores for both indications.

In schizophrenia trials, the mean body weight (83 kg vs. 72 kg) and BMI (29 vs. 25) were higher in patients in NA trials and NA predominant multi-regional(MR) trials compared to those in foreign-region predominant MR trials. Treatment effects decreased as body weights increased in NA trials. In foreign-region predominant MR trials, there were higher proportions of females (40% vs. 22-27%) and Asians (21% vs. 1.3-8%) than in NA trials and NA predominant MR trials.

Detail findings from these two databases will be presented and the implications on trial design and conduct will be further discussed.

Learning Objectives:
- Participants will learn how trial design features can affect study results.
- Participants will identify important factors in the design and conduct of global trials.

Literature References:
PANEL OVERVIEW:
FIELD TRIAL TESTING OF PROPOSED REVISIONS TO DSM-5
Darrel Regier¹, MD, William Narrow¹, MD, Eve Mościcki¹, David Kupfer¹, MD
¹American Psychiatric Association, ²University of Pittsburgh Medical Center

This session will provide audiences with an overview of the field trials to test proposed revisions to DSM-5. Included will be a summary of the design and approach, general findings, and outcomes specific to the large-scale medical and academic site settings as well as the routine clinical practice settings. Discussion will cover outcomes related to diagnostic criteria as well as findings related to testing of proposed dimensional assessments.

Learning Objectives:
- To describe the overall design of the two DSM-5 Field Trials and their objectives in the DSM-5 revision process
- To explain outcomes assessed in the field trials, including that of diagnostic criteria and dimensional assessment
- To provide examples of specific findings from the field trials
- To discuss the potential ways in which findings from the field trials may impact the future of clinical care using DSM-5

DSM-5 FIELD TRIALS IN ACADEMIC OR LARGE CLINICAL SETTINGS
Darrel A. Regier, MD
American Psychiatric Association, Arlington, VA

In 2010, the APA initiated testing of proposed changes to DSM-5 across 11 medical and academic centers. Over the course of the following 12 months, these institutions gathered data on the reliability, feasibility, and clinical utility of draft diagnostic criteria and other proposed changes to DSM-5. Their findings played a significant role in informing decisions by the 13 DSM-5 Work Groups, and the novel, innovative method of data collection used in the DSM-5 Field Trials represents advancement beyond the field testing strategies utilized during previous revisions of the manual. This presentation will share with audience members a synopsis of pertinent findings from these field trials, including data on the reliability of proposed diagnostic revisions as well as the clinical utility and feasibility of the draft changes. Detailed findings from field tests of select disorders will be shared. Discussion will include: descriptions and rationale of the proposed revisions, statistical results, and a review of potential implications of adopting (or not adopting) particular disorder changes, both clinically as well as in other relevant contexts (e.g., research, insurance coverage, etc.).

Learning Objectives:
- Audiences will be able to describe some of the general findings from field testing the proposed revisions to DSM-5.
- Audiences will be able to identify the ways in which clinical utility, feasibility, and reliability were assessed in large academic-medical site field trials.

Literature References:
DIMENSIONAL MEASURES IN PSYCHIATRIC DIAGNOSIS: RESULTS FROM THE DSM-5 FIELD TRIALS

William E. Narrow, MD, Diana E. Clarke, PhD, Darrel A. Regier, MD
American Psychiatric Association, Arlington, VA

The addition of dimensional measures to DSM-5 represents one of the manual’s most significant departures from the current diagnostic system. Dimensional assessments were proposed as a method to address some of DSM-IV’s known shortcomings, including the representation of psychiatric disorders as entities that fall neatly into discrete categories. Although commonly used in clinical research, dimensional approaches are not standard in psychiatric patient care. Developers of DSM-5 are hopeful that the proposed integration of dimensional assessments with categorical diagnoses may help address this gap between science and practice. This presentation will describe findings from the DSM-5 field trials of proposed cross-cutting and diagnosis-specific severity measures, with specific attention given to results from the trials of Bipolar Disorder, Posttraumatic Stress Disorder, and the World Health Organization Disability Assessment Schedule. Topics will include a brief overview and rationale of dimensional strategies that were tested, and results from the academic field trial sites, including test-retest reliability, clinical utility, and feasibility of the proposed measures. Clinical implications of integrating dimensional and categorical approaches to diagnosis in DSM-5 will be discussed.

Learning Objectives:
- To understand the relationship between categorical diagnoses and dimensional assessments in DSM-5
- To learn the test-retest reliability, feasibility and clinical utility of selected dimensional measures in the DSM-5 Field Trials

Literature References:

TESTING DSM-5 IN ROUTINE CLINICAL PRACTICE SETTINGS

Eve K. Moscicki, ScD, MPH
American Psychiatric Institute for Research and Education, Arlington, VA

The DSM-5 Field Trials in Routine Clinical Practice Settings (RCP) examined the feasibility, clinical utility, and sensitivity to change of the proposed DSM-5 diagnostic criteria and dimensional assessment measures as used by individual clinicians in routine clinical practice settings, representing the first time in the history of the DSM that the proposed diagnostic criteria were tested outside of academic settings. In another first, disciplines outside of psychiatry were invited to participate. This presentation will provide an overview of the design, sampling, procedures, and major findings for this important component of the DSM-5 Field Trials. Study participants included two samples of clinicians. The first was a representative sample of over 1,200 randomly selected general, child and adolescent, geriatric, addiction, and consultation-liaison psychiatrists. The second sample included nearly 4,000 clinicians from six disciplines who volunteered to participate in the field trials. Volunteers included psychiatrists, advanced practice psychiatric-mental health nurses, clinical psychologists, clinical social workers, licensed counselors, and marriage and family therapists. All participating clinicians had to meet strict eligibility criteria in order to participate. Eligible clinicians completed web-based DSM-5 training, including practice with the REDCap electronic data capture system, and enrolled at least one new and one existing patient into the Field Trial. Data characterizing the representative and volunteer samples of clinicians will be presented, including clinical discipline, specialty, caseload, nature of practice, practice setting, and patient caseload characteristics. The presentation will include a summary of major findings and a brief discussion of the unique challenges, opportunities, and successes found in implementing a large-scale scientific endeavor in small-scale settings.

Co-authors: William A. Narrow, M.D., M.P.H.; Lisa Countis; Farifteh F. Duffy, Ph.D.; Joyce C. West, Ph.D., M.P.P.; Donald S. Rae, M.A.; S. Janet Kuramoto, Ph.D., M.S.C.; Diana E. Clarke, Ph.D.; Darrel A. Regier, M.D., M.P.H.

Learning Objectives:
- Audiences will be able to identify some of the practical challenges and solutions in conducting field trials in routine clinical practice settings.
- Audiences will be able to describe some of the general findings from the DSM-5 Field Trials in Routine Clinical Practice Settings.

Literature References:
Identifying Biomarkers for Personalizing the Treatment of Depression: Implementation of Study Design and Initial Results in Subtype, Mechanism and Psychological Fields: AN iSPOT-D Report

Evian Gordon, PhD, Emit Etkin, MD, Leanne Williams, PhD, Kateri McRae, PhD

‘Brain Resource Ltd., ‘Stanford University, ‘University of Sydney, ‘University of Denver

Clinically useful treatment moderators of Major Depressive Disorder (MDD) are yet to be identified. The aim of iSPOT-D is to identify pretreatment measures that predict or moderate MDD treatment response or remission to escitalopram, sertraline or venlafaxine and develop a model that incorporates multiple predictors and moderators. Initial findings (1008 MDD participants) are in the areas of subtype, mechanism (MRI) and psychological analyses.

Increased comorbid anxiety, indicative of greater impairments in regulation of negative emotion, is a key negative predictor of treatment response. Thus, anxiety is an ideal target for novel interventions such as those for improving emotion regulation, which is abnormal in anxiety.

MRI studies found that compared to controls, MDD participants show consistent hypoactivation of the dorsolateral and dorsomedial prefrontal cortex during cognitive tasks and explicit emotion processing, and hyperactivation in the dorsomedial prefrontal regions during implicit non-conscious emotion processing. Activations in both regions correlated with behavioral and clinical symptom measures in MDD. Prefrontal dysfunction is an MDD feature seen across multiple cognitive and emotion processing tasks. Clinical implications of imaging results are to be considered in the context of outcomes from other measures.

Participant use of two emotion regulation strategies were tested pre- and post-treatment. Depressed participants used expressive suppression less frequently and cognitive reappraisal more frequently following treatment. Changes in use of suppression and reappraisal were independently associated with better treatment outcomes. Thus, it appears that successful pharmacological treatment for depression not only results in direct reduction of symptoms related to negative affect, but is also associated with a shift to a more adaptive emotion regulation profile.

Learning Objectives:

- Current treatment response and the potential improvements by identification of biomarkers.
- Identification of areas that may affect treatment response – initial results.

Protocol Design and Initial Results from the International Study to Predict Optimized Treatment in Depression: The iSPOT-D Study

Evian Gordon, PhD
Brain Resource Ltd., San Francisco, CA

Background: Clinically useful treatment moderators of Major Depressive Disorder (MDD) have not yet been replicated, although some baseline predictors of treatment outcome have been proposed. The aim of iSPOT-D is to identify pretreatment measures that predict or moderate MDD treatment response or remission to escitalopram, sertraline or venlafaxine; and develop a model that incorporates multiple predictors and moderators.

Methods: The International Study to Predict Optimized Treatment – in Depression (iSPOT-D) is a multi-centre, international, randomized, prospective, open-label trial. It is enrolling 2016 MDD outpatients (ages 18–65) from primary or specialty care practices (672 per treatment arm; 672 age-, sex- and education-matched healthy controls). Study-eligible patients are antidepressant medication (ADM) naïve or willing to undergo a one-week washout of any non-protocol ADM, and cannot have had an inadequate response to protocol ADM. Baseline assessments include symptoms; distress; daily function; cognitive performance; electroencephalogram and event-related potentials; heart rate and genetic measures (and 25% have MRI and fMRI undertaken). A subset of these baseline assessments are repeated after eight weeks of treatment. Outcomes include the 17-item Hamilton Rating Scale for Depression (primary) and self-reported depressive symptoms; social functioning, quality of life, emotional regulation, and side-effect burden (secondary). Participants may then enter a naturalistic telephone follow-up at weeks 12, 16, 24 and 52. Results from the first half of the sample will be presented and used to identify potential predictors and moderators. The second half of subjects will be used to replicate and confirm predictors and moderators.

Discussion: First enrolment was in December 2008, and is ongoing. iSPOT-D evaluates clinical and biological predictors of treatment response in the largest known sample of MDD collected worldwide.

Trial registration: International Study to Predict Optimised Treatment in Depression (iSPOT-D)
ClinicalTrials.gov Identifier: NCT00693849
URL: http://clinicaltrials.gov/ct2/show/NCT00693849?term=In

Learning Objectives:

- Context of brain-based Personalized Medicine
- Translational clinical Biomarkers for diagnosis and treatment of depression

Literature References:

UNDERSTANDING ANXIETY AND ITS RELATIONSHIP TO TREATMENT RESPONSE IN DEPRESSION: AN ISPD-O REPORT

Amit Etkin MD
University of Stanford / VA, Palo Alto, CA

Anxiety and depression are closely related, and often comorbid clinical states, whose interplay is important for understanding dysfunction in mood disorder patients, as well as response to treatment. Prior work, primarily from studies of antidepressant medications, has suggested that baseline anxiety in depressed patients is a general predictor of poor treatment response. Controversies exist, however, regarding whether anxiety is a unique clinical predictor independent of the increased medication side effects typically reported in anxious patients, of the presence of a comorbid anxiety disorder (vs. a dimension of dysfunction existing independently of DSM-based diagnosis), or of prior treatment failure (vs. treatment-naive). More importantly, the neurobiological bases of anxiety, as contrasted with depression, are only now being directly investigated across comparable clinical cohorts, and it is presently unknown which neural abnormalities associated with anxiety are relevant for its relationship with treatment outcome. In this talk, I will present clinical, fMRI and EEG data from patients with MDD and a range of anxiety levels and comorbidities from the International Study to Predict Optimized Treatment in Depression (ISPD-O), a biomarker-coupled outcome study in which 1008 depressed patients were randomized to one of three different antidepressants. Baseline anxiety was found to be an important clinical predictor of poor response to antidepressant medication, halving remission rates between low and high anxiety subjects. This relationship was independent of overall depression severity or the presence of a comorbid anxiety disorder, and did not interact with history of prior treatment failure. These clinical data outcomes will be discussed in the context of neurobiological data from fMRI and EEG, together yielding important new insights into the neural bases of anxiety and depression, and how their interplay impacts treatment outcome.

Learning Objectives:
• Explain the relationship of anxiety to outcome with antidepressants
• Describe the neural correlates of anxiety in depression.

Literature References:

PREFRONTAL DYSFUNCTION IN MAJOR DEPRESSION: PRELIMINARY FUNCTIONAL MAGNETIC RESONANCE IMAGING RESULTS

Leanne Williams, PhD
University of Sydney, Westmead, NSW, Australia

Objectives: Understanding the biological basis of major depressive disorder (MDD) is needed to advance evidence-based diagnosis and treatment. The aim of the International Study to Predict Optimized Treatment in Depression (ISPD-O) is to identify biological pretreatment measures that distinguish MDD, and predict or moderate response to escitalopram, sertraline or venlafaxine (1).

Method: ISPD-O is enrolling 2016 MDD ambulatory-care patients (ages 18-65, 672 per treatment arm; plus 672 age-, sex- and education-matched healthy controls). Study-eligible patients are antidepressant medication (ADM) naïve or willing to undergo a one-week wash-out. Baseline assessments include symptoms, functional status, cognition and emotion task performance, electroencephalogram and event-related potentials; heart rate and genetic measures. 10% of these patients are assessed with structural and functional brain imaging. Standardized protocols evaluate cognitive (selective attention, sustained attention-working memory and impulsivity-inhibition) and emotion (explicit and implicit) during functional magnetic resonance imaging recording. The first planned outcomes are for 15% of patients (n=22) versus matched healthy controls from the ISPD-O imaging subset.

Results: Compared to controls, MDD patients showed consistent hypoactivation of the dorsolateral and dorsomedial prefrontal cortex during cognitive tasks. A similar profile of hypoactivation was found during explicit emotion processing. By contrast, hyperactivation in the dorsomedial prefrontal regions was observed during implicit non-conscious emotion processing. Activations in both these prefrontal regions were correlated with behavioral and clinical symptom measures in MDD.

Conclusion: Prefrontal dysfunction is a feature of MDD seen across multiple cognitive and emotion processing. The clinical implications of imaging results are to be considered in the context of outcomes from other measures. The first 50% of patients (n=1008) completed the study by December 2010. ISPD-O is evaluating biological and clinical predictors in the largest known sample of MDD collected worldwide.

Learning Objectives:
• Understanding the brain circuitry involved in major depressive disorder
• Knowing if there is a consistent frontal impairment in depression affecting cognition and emotional functions
• Identifying brain regions relevant to antidepressant treatment response
• Novel trial design for including biological as well as clinical measures

Literature References:
EMOTION REGULATION STRATEGIES AND TREATMENT RESPONSE IN MAJOR DEPRESSIVE DISORDER: AN ISOT-D REPORT

Kateri McRae\textsuperscript{1}, PhD, James J. Gross\textsuperscript{2}, PhD

\textsuperscript{1}University of Denver, Denver, CO, \textsuperscript{2}Stanford University, Stanford, CA

Anti-depressant medication (ADM) is thought to reduce depressive symptoms through direct action on the neural regions that process negative information and affect. By this account, pharmacological treatment for depression should have little effect on the effortful strategies that patients use to reduce negative affect. We measured patient use of two emotion regulation strategies, expressive suppression and cognitive reappraisal, before and after the administration of ADM. We observed significant changes in the frequency with which patients used these strategies before and after treatment: Depressed patients used expressive suppression less frequently and cognitive reappraisal more frequently following treatment. Additionally, the magnitude of change was related to treatment outcome: Larger decreases in suppression use and larger decreases in reappraisal use were associated with better treatment outcomes. The effects of change in expressive suppression and cognitive reappraisal on treatment outcome were independent. We interpret these results as evidence that successful pharmacological treatment for depression does not only result in direct reduction of symptoms related to negative affect, but is also associated with a shift to a more adaptive emotion regulation profile.

Learning Objectives:
- Participants will be able to discuss a potential psychological mechanism by which ADM improves depressive symptoms.
- Participants will outline the role of emotion regulation in ADM treatment outcome.

Literature References:
PANEL
8:30 A.M. - 10:00 A.M.

PANEL OVERVIEW:
TARGETS TO TREAT ALCOHOL DEPENDENCE: NEW HUMAN STUDIES
Raye Litten, PhD, Rajita Sinha, PhD, Bankole Johnson, MD, PhD
National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD,
Foundations Fund Professor of Psychiatry, Neurobiology and Child Study, New
Haven, CT, University of Virginia School of Medicine, Charlottesville, VA

During the past decade, solid advances have been made in medications to
treat alcohol dependence. Currently, four medications have been approved
by the FDA for alcohol dependence. Because of the heterogeneous and
behavioral complexities associated with alcoholism, these medications do not
work for everyone. To identify the next generation of medications, agents that
target different molecular sites in the brain are being evaluated in human
studies. In this panel session, Dr. Joanne Fertig will describe the efficacy and
safety results from a multisite trial of the anticonvulsant levetiracetam in
alcohol-dependent subjects. The use of anticonvulsants, which target the
GABA and glutamate systems, have demonstrated potential efficacy in treating
alcohol dependency. Dr. Rajita Sinha will present new findings on the effects of
the alpha-1 noradrenergic antagonist prazosin on stress-induced alcohol
craving, anxiety, and brain stress dysregulation in alcohol dependent
individuals. Finally, Dr. Bankole Johnson will present pharmacogenetic
approaches in predicting treatment outcome for ondansetron, a 5-HT3
antagonist, in alcohol dependent patients. In particular, Dr. Johnson will, for
the first time, demonstrate an interaction between genetic variants that
significantly enhanced the effect size of ondansetron. As alcohol research
continues to unravel the biological mechanisms that underlie alcohol
dependence, leading to the discovery and validation of new molecular targets
for drug development, new more effective medications will be developed. As a
result, affected individuals and their families will be spared myriad, costly
alcoholism-associated medical, psychological, social, economic, and personal
problems.

Learning Objectives:
• Identify various molecular targets for the treatment of alcohol dependence
• Determine how stress dysregulation increases alcohol relapse and the
efficacy of medications that target the stress system
• Identify different genetic variants and how they interact to enhance
treatment outcome: identify the cutting-edge research approaches in
developing medication to treat alcohol dependence

A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL ASSESSING THE EFFICACY
OF LEVETIRACETAM EXTENDED-RELEASE IN VERY HEAVY DRINKING
ALCOHOL-DEPENDENT PATIENTS
Raye Z. Litten, PhD, Joanne Fertig, PhD
National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD

In this double-blind, randomized, placebo-controlled clinical trial, 130 alcohol-
dependent patients who reported very heavy drinking were recruited across 5
clinical sites. Patients received either levetiracetam extended-release (XR) or
placebo and a Brief Behavioral Compliance Enhancement Treatment
intervention. Levetiracetam XR was titrated during the first 4 weeks to 2000
mg/day. This target dose was maintained during weeks 5 through 14 and was
tapered during weeks 15 and 16.

Results: No significant differences were detected between the levetiracetam
XR and placebo groups in either the primary outcomes (percent heavy drinking
days and percent subjects with no heavy drinking days) or in other secondary
drinking outcomes. Treatment groups did not differ on a number of
nondrinking outcomes, including depression, anxiety, mood, and quality of life.
The only difference observed was in alcohol-related consequences. The
levetiracetam XR treatment group showed significantly fewer consequences
than did the placebo group during the maintenance period (p = 0.02).
Levetiracetam XR was well tolerated, with fatigue being the only significantly
elevated adverse event, compared with placebo (53% vs. 24%, respectively; p =
0.001).

Conclusions: This multistate clinical trial showed no efficacy for levetiracetam
XR compared with placebo in reducing alcohol consumption in heavy drinking
alcohol-dependent patients.

Learning Objectives:
• Understand the utility of the anti-seizure medication levetiracetam in the
treatment of alcohol dependence.
• Understand the relationship between drinking and alcohol related
consequences.

Literature References:
• Sarid-Sepal O, Piechniczek-Ruczek, J, Knapp, C, Afsar, M, Devine,E,Sickles,L,
levetiracetam on alcohol consumption in alcohol-dependent subjects: an open
• Muller CA, Schafer M, Sanchaider S, Helimann HM, Hinpeter A, Volkmar K,
EFFECTS OF THE ALPHA-1 NORADRENERGIC ANTAGONIST, PRAZOSIN ON STRESS-INDUCED ALCOHOL CRAVING, ANXIETY AND BRAIN STRESS DYSREGULATION IN ALCOHOL DEPENDENT INDIVIDUALS

Rajita Sinha, PhD
Foundations Fund Professor of Psychiatry, Neurobiology and Child Study, New Haven, CT

Background: Stress and anxiety play an important role in development of alcoholism and in alcohol relapse. Our previous research has consistently shown that laboratory-based stress and alcohol cue exposure increase alcohol craving, negative emotion and anxiety in alcohol dependent individuals. Furthermore, stress-induced and alcohol cue-induced craving is predictive of subsequent relapse outcomes in alcohol dependence. Previous research indicates that noradrenergic agents such as Prazosin decreases alcohol withdrawal and may also be of benefit in decreasing alcohol intake in laboratory animals and humans.

Method: Double blind, placebo-controlled laboratory studies using Prazosin (0.16mg/day) in alcoholics were conducted to examine their effects on subjective negative emotion, alcohol craving, physiological and endocrine responses during brief imagery exposure to personalized scripts of stressful, drug cue-related and neutral-relaxing situations. Preliminary data from functional magnetic resonance imaging (fMRI) study of Prazosin effects on neural correlates of stress-induced alcohol craving states is also being examined.

Results: Findings indicate that Prazosin significantly decreased stress and alcohol cue-induced craving and anxiety relative to responses in the neutral condition in treatment engaged alcoholics. Furthermore, individuals with lifetime history of co-morbid anxiety disorders showed better effects of Prazosin on stress-induced alcohol craving, anxiety and biological stress dysregulation. Neural correlates of such decreases in stress and cue-induced alcohol craving were observed as increased activation in the anterior cingulate and medial and lateral orbitofrontal cortex in Prazosin versus placebo alcohol dependent individuals.

Discussion: These results provide some insight into the possible mechanisms by which Prazosin may have beneficial effects in the treatment of alcohol dependence. Findings indicate that Prazosin may decrease anxiety, stress-induced alcohol craving and normalize stress dysregulation by improving prefrontal regulatory function of stressful and other arousal states. The findings support development of noradrenergic agents such as Prazosin to target alcohol craving and stress dysregulation in alcoholism relapse risk. (Supported by NIH Grants: R01-AA013892; PL1-DA024859; UL1-DE019586, UL1-RR024139).

Learning Objectives:
- To provide new information on role of stress biology and stress-induced craving in alcohol relapse
- To provide new data on therapeutics to reduce stress pathophysiology in alcoholism to improve relapse outcomes, using Prazosin as a case in point.

Literature References:

PHARMACOGENETIC APPROACH TO OPTIMIZE TREATMENT RESPONSE TO ONDANSETRON IN ALCOHOL-DEPENDENT PATIENTS

Bankole Johnson, MD, PhD
University of Virginia, Charlottesville, VA

Pharmacogenetic treatments are key components of a personalized medicine approach toward finding efficacious pharmacotherapies for alcohol dependence because of their potential to optimize therapeutic response and limit inter-individual variability. The serotonin transporter (5-HTT) gates approximately 60% of neuronal serotonin function. Specific genetic variants of the 5-HTT gene have been associated with prediction of alcohol craving and with major differences in serotoninergic expression. They could, therefore, be an important target for clinical treatment. We sought to demonstrate that ondansetron is an efficacious pharmacogenetic treatment for alcohol dependence. Alcohol-dependent individuals (N=283) were randomized by genotype in the 5’ O€ regulatory region of the 5-HTT gene (LL/LS/SS) in a controlled, double-blind clinical trial. Additional genotyping was performed for another functional single nucleotide polymorphism (SNP), rs1042173 (T/G) in the 3’ O€ untranslated region of the 5-HTT gene, and for rs11512022 (A/G) and rs17614942 (A/C) in the HTR3A and HTR3B genes respectively. The HTR3A and HTR3B genetic variants were included in the analyses because ondansetron targets primarily 5-HT3A/B receptor complexes on post-synaptic neurons. Subjects were given either the specific 5HT3 antagonist ondansetron (4 fEq/kg twice daily) or placebo, along with weekly standardized cognitive behavioral therapy, for 11 weeks. Ondansetron’s efficacy among the various genotypes was examined using new endpoints, including * gcompletor analyses h. Differences in genetic variation predicted the improved abstinence and the reduction in drinking severity that were observed after the administration of ondansetron. Specifically, individuals who carried the LL/TT, A/G, and/or A/C genotypes showed improvements in drinks per drinking day, percentage of heavy drinking days, and percentage of days abstinent with ondansetron treatment. This knowledge on the epistatic effects of the 5-HTT, HTR3A, and HTR3B genes on ondansetron treatment response among alcohol-dependent individuals could lay the groundwork for ondansetron’s role in the pharmacogenetic treatment of alcohol-dependent individuals.

Learning Objectives:
- To receive an introduction to personalized medicine approaches for treating alcohol dependence
- To gain an understanding of how molecular differences can affect psychological factors, including the motivation to drink, and how this can be affected by medicinal or psychological interventions

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