



PROGRAM SESSION ABSTRACTS

50TH ANNIVERSARY MEETING

June 14 - 17, 2010

Boca Raton Hotel

Boca Raton, FL



50TH

**Anniversary
Meeting**



| | |
|-----------------------------|-------|
| Monday, June 14 | |
| Workshops 1–6 | 1–16 |
| Tuesday, June 15 | |
| Plenary Session I | 17 |
| Panel 1 Part I | 18–20 |
| Panel 1 Part II | 21 |
| Panels 2–6 | 22–34 |
| Wednesday, June 16 | |
| Plenary Session II | 35 |
| Symposium | 36–37 |
| Panel 7 | 38–39 |
| Individual Research Reports | 40–42 |
| Workshop 7 | 43–46 |
| Panel 8–11 | 47–56 |
| Thursday, June 17 | |
| Plenary Session III | 57 |

Sources of funding for program session presenters are included with your conference materials.

The NCDEU Meeting’s primary purpose is to facilitate the dissemination and exchange on developments and continuing educational updates in clinical interventions research. The materials presented at this conference, including viewpoints expressed by National Institute of Mental Health (NIMH) staff members, do not necessarily reflect the opinions, official policy or position of the NIMH or the U.S. Government. Likewise, all materials appearing in the NCDEU Abstract Book, except where otherwise noted, are in the public domain and may be reproduced or copied without requesting the author’s permission.



Workshop 1

Models for Multi-Center Clinical Trials: History, Contemporary Practice and Ideas for the Future
9:00 a.m. – 12:00 p.m.

Workshop Overview

Nina R. Schooler, Ph.D.

State University of New York, Downstate Medical Center

Joanne B. Severe, M.S.

National Institute for Mental Health

From the beginning, the field of clinical psychopharmacology has incorporated multi-center studies. This workshop is designed to bring together information from the earliest days, through current practice and methods that are beginning to be adopted. The primary goal is to see whether, as modern technology is adopted, strengths of earlier periods can be integrated into randomized trials.

History: The Early Clinical Drug Evaluation Units (ECDEU) program was an ambitious model that brought psychopharmacology investigators together to share information about new agents, trials in process and accomplishments and methods for recruiting, assessing and analyzing data. The National Institute of Mental Health (NIMH) supported Biometric Laboratory Information Processing System (BLIPS) was a unique resource that provided a library of tools and a data analysis system for comparison across studies. A presenter will review with an emphasis on aspects of the program that are relevant for modern trials.

Contemporary Practices: Two presentations will focus on complementary contemporary practices. The first will review the current model of NIMH-initiated collaborations based on identification of high priority research questions and use of contracts and establishing diagnosis-based research networks. The next presenter will consider a second approach that is based on identification of research questions by investigators in the field who join together to create independent research networks that are supported by either single grants or what are known as collaborative R01s.

Ideas for the Future: Future trials will likely use settings such as health care networks and other primary care settings. Conducting trials in these settings will present new challenges. A presenter will discuss novel statistical approaches and item pooling methods that may allow for more efficient subject selection and assessment. The final presenter will focus on methods for increasing efficiency and accuracy in data collection and data management.

Learning Objectives:

- Review current models for NIMH clinical trials in the context of the history of ECDEU and New Clinical Drug Evaluation Units (NCDEU)
- Build on current approaches by identifying trends for future trials in terms of settings, recruitment, assessment and data acquisition and management

Early Clinical Drug Evaluation Units (ECDEU) and Biometric Laboratory Information Processing System (BLIPS): An Early Data Collection and Management Model for Integration across Clinical Sites

Jerome Levine, M.D.

Formerly of the Nathan S. Kline Institute for Psychiatric Research and New York University School of Medicine

Imagine a Time When:

- Psychoanalysis and psychotherapy were the primary psychiatric therapies.
- Treatment of psychiatric disorders with medication was deemed adjunctive at best and unethical at worst.
- Medications could be marketed without proof of efficacy.
- Controlled clinical trials were just beginning to be used in other areas of medicine.
- There were few clinical investigators who were carrying out clinical studies of investigational psychiatric medications.
- There were no widely accepted clinical trial designs, diagnostic criteria or outcome measures.

Then came Early Clinical Drug Evaluation Units (ECDEU), New Clinical Drug Evaluation Units (NCDEU), and Biometric Laboratory Information Processing Systems (BLIPS):

The National Institute of Mental Health (NIMH) gave multi-year grants to investigators to carry out clinical studies of investigational or marketed medications of their choice in psychiatric disorders of their choice using research designs and clinical instruments of their choice. These ECDEU investigators were required to meet together (closed meetings) every six months to present their methods and study results. Consensus regarding the efficacy and safety of medications was sought by replication of findings across sites. Investigators gradually settled on preferred study designs and diagnostic and outcome instruments (rating scales). NIMH staff along with a contract supported Biometric Laboratory at GW University codified the study instruments and scales into the ECDEU Assessment Manual. ECDEU investigators chose from this cafeteria of study instruments those that were appropriate for their individual studies. The Biometric Laboratory distributed the instruments as Case Report Forms to investigators who used them in studies and returned them to the Biometric Laboratory for data management and statistical analysis using the BLIPS. The standardized reports presented at the ECDEU/NCDEU meetings made it possible to compare study results across different research settings without using identical protocols or instruments. The widespread use of these instruments and data analysis methods provided the basis for Food and Drug Administration (FDA) guidelines for the conduct of clinical trials for psychopharmacologic agents.

Learning Objectives:

- Understand the historical context in which ECDEU/NCDEU/BLIPS developed
- Understand the possibility of using standardized methods and replication to study efficacy and safety of psychopharmacologic agents

Literature References:

- Levine J. History and role of guidelines and guidance for drug evaluation. In: Prien, RF, Robinson, DS. Clinical evaluation of psychotropic drugs. New York: Raven Press Ltd; 1994.
- Guy W, et al. A data processing system for psychotropic drug evaluation. Arch Gen Psychiatry 1970;23:454-63.

Workshop 1

Models for Multi-Center Clinical Trials: History, Contemporary Practice and Ideas for the Future

9:00 a.m. – 12:00 p.m.

NIMH Funding Mechanisms for Multi-Site Clinical Trials

Joanne B. Severe, M.S.

National Institute of Mental Health

Adequate resources to conduct clinical trials are required to advance knowledge in treatment development and comparative effectiveness, and to translate it to improved care. Over the years the National Institute of Mental Health (NIMH) has used various funding mechanisms to support clinical trials that purport to do just that. In 1998, NIMH launched a broad program of large-scale effectiveness trials to address important public health questions in “real-world” populations. The research contracting mechanism was used for the first time to support such trials in mental health. The model that emerged was a central contract awarded to a single primary investigator (PI), who would then create an organization that included a national coordinating center; a data management and statistical center; clinical sites where patients were enrolled, treated, and assessed; and an executive center to manage the organization and assume overall responsibility. Two key features of these contract-supported trials were that clinical sites were paid based on subject enrollment and retention and data collection, and the contract PI had administrative flexibility to discontinue non-productive sites and/or add new sites. After the trials were completed, these large clinical trial infrastructures evolved into the NIMH clinical trials networks, also supported by contract funds. The model proved successful in that trials met their enrollment goals, finished on time and produced high-quality data that addressed the intended questions.

Learning Objectives:

- Understand how funding mechanisms can affect infrastructure and conduct of multi-site clinical trials
- Invite discussion of possible new or alternative funding mechanisms that could enable clinical trials to be conducted more efficiently

Literature References:

Lebowitz BD, et al. Approaches to multisite clinical trials: the National Institute of Mental Health perspective. *Schizophr Bull* 2003;29(1):7–13.
Special section on the implications of STAR*D. *Psychiatr Serv* 2009 Nov;60:1437–67.

Multi-Center Collaborations Established by Investigator Groups: The “Collaborative R01”

Nina R. Schooler, Ph.D.

State University of New York, Downstate Medical Center

Over the decades since the Early Clinical Drug Evaluation Units (ECDEU) and New Clinical Drug Evaluation Units (NCDEU) were established, it has become increasingly clear that multi-center studies are required in order to adequately address clinical questions regarding treatments. Multi-site studies allow generalization across centers and adequate subject enrollment in a time frame that is required by the field to address questions of high clinical significance. One relatively recent approach that has been used is represented by the identification of a clinical question and the creation of a group to address it independent of a centralized authority, be that a government agency or a pharmaceutical sponsor. Sources of support for such studies include investigator initiated grants from the pharmaceutical industry, linked grants or single grants with sub-contracts from the National Institute of Mental Health (NIMH). These studies represent a response from the field to perceived needs. The models followed by these investigator groups vary. The presentation will review strengths and weaknesses of these models to set the stage for consideration of the range of models that will be needed in future.

Learning Objectives:

- Understand how multi-center collaborations are developed and sustained
- Recognize advantages and disadvantages of hierarchical and egalitarian collaborative models

Literature References:

Kane JM, et al. Clozapine and haloperidol in moderately refractory schizophrenia: a six-month randomized and double-blind comparison. *Arch Gen Psychiatry* 2001;58(10):965–72.
Buchanan RW, et al. The cognitive and negative symptoms in schizophrenia trial (CONSIST); the efficacy of glutamatergic agents for negative symptoms and cognitive impairments. *Am J Psychiatry* 2007;164:1593–1602.

Workshop 1

Models for Multi-Center Clinical Trials: History, Contemporary Practice and Ideas for the Future
9:00 a.m. – 12:00 p.m.

Using Technologies in Clinical Research Studies

James A. Robinson, M.S.

Nathan S. Kline Institute for Psychiatric Research

Technologies have been used in clinical research studies for almost as long as the New Clinical Drug Evaluation Units (NCDEU) has held conferences. Since the initial use of computers, more and better technologies have become available that can be effectively used in clinical research studies, and there is an increasing trend to adopt them. Using available, proven technologies will improve the efficiency of conducting research studies. This presentation will discuss and illustrate technologies that are ready and available for use. Electronic Data Capture (EDC) systems, the most frequently used technology in clinical research studies today, will be discussed. Technological features of EDC systems will be illustrated that provide the following advantages in conducting clinical research studies:

- (1) expediting the initiation of a study;
- (2) increasing the completeness and accuracy of data;
- (3) assisting in the cleaning of data and resolving of data inconsistencies and discrepancies;
- (4) expediting the locking of a database and decreasing the time to begin data analyses; and
- (5) reducing the time required to complete a study.

The use of audio computer assisted self-interviewing (ACASI) and computer assisted interviewing (CAI) technologies will be reviewed. The use of web based interviewing systems will be presented to illustrate real time, confidential data collection, standardized interviewing methodologies, reduced effort in the management of data and overall cost effectiveness. Because of the increased emphasis on patient reported outcomes (PROs) and the collection of such data electronically, the use of hand held devices and interactive voice response devices will also be presented. The advantages of the use of hand held technologies and interactive voice response systems will be reviewed in detail.

Learning Objectives:

- Provide an understanding of the technologies that are available and can be immediately used in clinical research studies
- Illustrate the advantages and disadvantages of using specific technologies in clinical research studies

Literature References:

- Wolford G, et al. A clinical trial comparing interviewer and computer-assisted assessment among clients with severe mental illness. *Psychiatr Serv* 2008;59(7):769–74.
- El Emam K, et al. The use of electronic data capture tools in clinical trials: web-survey of 259 Canadian trials. *J Med Internet Res* 2009 Mar;11(1):e8.

The Future of Psychiatric Measurement

Robert D. Gibbons, Ph.D.

University of Illinois, Chicago

Mental health measurement has been based primarily on subjective judgment and classical test theory. Typically, impairment level is determined by a total score, requiring that all respondents be administered the same items. An alternative to full scale administration is adaptive testing in which different individuals may receive different scale items that are targeted to their specific impairment level. Within adaptive testing, individuals' initial item responses are used to determine a provisional estimate of their standing on the measured trait (e.g., depression, anxiety) to be used for subsequent item selection. This form of testing has recently emerged in mental health research. Based on item response theory (IRT) procedures, estimates of items (e.g., difficulty, discrimination) and individuals (e.g., severity of depression) can be obtained to more efficiently identify suitable item subsets for each individual. This approach to testing is referred to as computerized adaptive testing (CAT) and is immediately applicable to psychiatric measurement problems. We have developed a CAT depression inventory (CAT-DI) that can be administered adaptively, such that each individual responds only to those items that are most appropriate to assessing his/her level of depression. The net result is that an individual is administered a small, optimal number of items without loss of measurement precision. The shift in paradigm is from small fixed length tests with questionable psychometric properties to large item banks from which an optimal small subset of items is adaptively drawn for each individual, targeted to their level of impairment. Rather than fixing the number of items administered, we fix the precision of measurement and adaptively administer a sufficient number of items to achieve a constant level of precision for all subjects. For longitudinal studies, the previous impairment estimate is then used as a starting point for the next adaptive test administration, further decreasing the number of items needed to be administered.

Learning Objectives:

- Learn about item response theory (IRT)
- Learn about computerized adaptive testing
- Discuss improved psychiatric measurement

Literature References:

- Gibbons RD, et al. Using computerized adaptive testing to reduce the burden of mental health assessment. *Psychiatr Serv* 2008;59:361–68.
- Gibbons RD, et al. Full-information item bi-factor analysis of graded response data. *Appl Psychologic Measurement* 2007;31:4–19.

Workshop 2

Enhancing Precision in Clinical Trials XIII

9:00 a.m. – 12:00 p.m.

Workshop Overview

Mark H. Rapaport, M.D.

Cedars-Sinai Medical Center and University of California, Los Angeles School of Medicine

Adam J. Haim, Ph.D.

National Institute of Mental Health

This year's workshop hews closely to the 50th Anniversary theme: Learning from the Past to Advance the Future of Mental Health Treatment. The last five decades have seen changes in clinical trials methods that affect precision in signal detection of efficacy and adverse events as well as enduring effectiveness of medications for psychiatric disorders. An overarching goal of this year's workshop is to discern how advances in computing, mathematics, neurosciences and nosology have impacted clinical trial design over the last 50 years, and what experts believe the next set of major advances will be. In keeping with the theme of where we have been, where we are now, and where we are going, four presenters will discuss:

- (1) the change in research philosophy as well as the advances in self-assessment methodology;
- (2) innovative new research tools that are the fruit of National Institute of Mental Health (NIMH)-funded small business innovation research (SBIR) and how such collaboration may change trial design;
- (3) the impact of changes in the type, number, and nature (one site, U.S., western Europe, versus truly international trials) and the impact on clinician evaluations;
- (4) how changes in computational technology and analytic tools have led to a radical shift in the trial design and statistical approaches; and
- (5) how the nature of outcome measures for trials has evolved from subject assessments to more object ratings to newer technology-assisted potential measures.

Each of the presentations will begin with an historical perspective, move to current trials methods and end with forecasts of future methods to enhance precision in clinical trials.

Learning Objectives:

- Understand appropriate roles for clinician- and self-report-assessments
- Recognize obstacles to implementation of new study designs and technologies
- Review alternative outcomes that may overcome present outcome limitations
- Review changes in statistical design that improve understanding of results
- Recognize the role technology may play in influencing data acquisition

Assessing Patients, Measuring Outcomes, and Evaluating Treatment Effects: Similarities, Differences, Strengths and Weaknesses of Clinician-Based Judgment, Computer-Automated Clinical Interviews and Patient-Reported Outcomes

James C. Mundt, Ph.D.

Healthcare Technology Systems, Inc.

Placebo-controlled, randomized controlled trials (RCTs) are the gold standard for evidence-based studies of treatment efficacy. Clinician-based evaluations of patient response to treatments for central nervous system disorders are primary outcome measures in most RCTs. Increasing numbers of failed trials in recent years has raised concerns about the standardization, reliability and validity of clinician-based outcome measures. Patient reported outcomes (PROs), administered on paper forms and/or electronically, have become increasingly popular and have gained regulatory acceptance for supporting labeling claims. Concerns regarding the development and validation of PROs; the comparability with established assessment instruments reliant upon clinical judgments of human raters; and evaluation of methodological utility in RCTs will be discussed.

Learning Objectives:

- Better understand the sources of measurement error and bias that may influence both clinician-based assessments and patient-reported outcomes
- Evaluate the strengths, weaknesses, and assumptions regarding the standardization of assessment procedures and presumed influences on signal detection

Literature References:

- Kobak KA, et al. Sources of unreliability in depression ratings. *J Clin Psychopharmacol* 2009 Feb;29(1):82–85.
- Mundt JC, et al. Is it easier to find what you are looking for if you think you know what it looks like? *J Clin Psychopharmacol* 2007 Apr;27(2):121–25.

Workshop 2

Enhancing Precision in Clinical Trials XIII

9:00 a.m. – 12:00 p.m.

Using New Information Technologies to Speed and Decrease the Cost of Clinical Trials**Benjamin B. Brodey, M.D., M.P.H.**
TeleSage, Inc.

TeleSage, Inc., with support from the National Institute of Mental Health (NIMH), has developed three new research tools to improve the quality of clinical research, decrease the cost of clinical trials and speed the translation of clinical research results into patient care, including (1) a computerized version of the Structured Clinical Interview for DSM Disorders (SCID); (2) item response theory (IRT)-based outcomes assessments; (3) large state-wide databases featuring high quality longitudinal outcomes assessments integrated into electronic health records. A fourth research tool, specifically software for computer adaptive testing (CAT) administration, is currently in development. The NetSCID (a web-based version of SCID) records individual diagnostic criteria endorsed by a research participant to a standard database, which may enable researchers to link specific diagnostic criteria to particular genetic markers, neuroanatomical findings or clinical interventions and their outcomes. In this way, it may be possible to determine the potential success of a given intervention based on a more detailed participant presentation using specific diagnostic criteria. IRT-based assessments and scoring increases the precision of outcome measurement relative to assessments developed using Classical Test Theory. As a result, it should be possible to achieve significant results using smaller samples. CAT facilitates the selective administration of the most informative survey items for a given individual, decreasing test burden and increasing the potential to recruit participants. The development of large state-wide databases may create the potential to rapidly test hypotheses using a more naturalistic data mining approach. Supported hypotheses can then be tested via rigorous, targeted prospective studies, thereby decreasing research costs and speeding the identification of effective interventions. It is our hope that these new research tools will improve not only clinical research, but also its impact on patient care. In addition, we challenge researchers to think about how these tools can be used in novel ways to improve clinical trials, as well as to explore the new ways that information technologies can be used as clinical research tools.

Learning Objectives:

- Explore how specific DSM diagnostic criteria data can be used to identify individuals who may be more likely to respond to an intervention than individuals for whom only a broader DSM diagnosis is recorded
- Learn how IRT can be used to increase the efficiency of clinical trials
- Learn about large statewide mental health outcomes databases that are available and can be used in preliminary 'naturalistic' studies to speed the translation of clinical research into practice

Literature References:

Flynn KE, et al. Incorporating item banks into clinical trials: investigator perceptions. *Clin Trials* 2008;5:575–86.

VanRegenmorter CJ, et al. Four ways to change behavioral healthcare—current knowledge network projects. Poster session presented at: National Council for Community Behavioral Healthcare Annual Conference. 2010 Mar 15; Orlando, FL.

The Enigma of Ratings Accuracy in Central Nervous System (CNS) Trials**Steven D. Targum, M.D.**
Oxford Bioscience Partners

The inherent subjectivity of most CNS symptom measurements contributes to inconsistent ratings that can adversely affect clinical trial outcomes. The increased globalization of CNS studies has magnified the ratings enigma due, in part, to the large number of trial sites creating a marked diversity of educational, cultural and clinical perspectives. This presentation will review the evolution of efforts to standardize site-based rater qualification and review the development of site-independent methods introduced to optimize trial outcomes. The current application of site-independent methods to verify patient validity and to improve signal detection will be critically examined using data from some recent studies. It is clear that the next generation of CNS trials will incorporate customized, site-independent quality assurance strategies to focus on patient validity prior to randomization and to improve ratings precision.

Learning Objectives:

- Examine the variables affecting ratings accuracy in global clinical trials
- Review innovative site-independent strategies to optimize CNS trial outcomes

Literature References:

Targum SD. Evaluating rater competency for CNS clinical trials. *J Clin Psychopharmacol* 2006;26:308–10.

Targum SD, et al. Redefining affective disorders: relevance for drug development. *CNS Neurosci Ther* 2008;14:2–9.

Fava M, et al. The problem of placebo response in clinical trials for psychiatric disorders. *Psychother Psychosom* 2003;72:115–27.

Workshop 2

Enhancing Precision in Clinical Trials XIII

9:00 a.m. – 12:00 p.m.

Evolution of Randomized Controlled Trials (RCT) Design and Analysis: A Half Century in the Making**Andrew C. Leon, Ph.D.**

Weill Medical College of Cornell University

In the fifty years since the initial Early Clinical Drug Evaluation Units (ECDEU) and New Clinical Drug Evaluation Units (NCDEU) meetings, there have been numerous advances in design and analysis for randomized controlled clinical trials. Here we examine the evolution of methods for randomized controlled trials (RCTs) such as strategies for attrition and missing data, multiplicity and multiple outcomes, sample size determination, and the choice of credible controls. The handling of subjects with incomplete data initially involved analyses of completers only and then implemented last observation carried forward as an imputation technique. Each approach makes rather untenable assumptions. More recently mixed-effects models have been used. This analytic strategy can include all available data on each randomized subject, thereby reducing bias and increasing power, precision, generalizability and feasibility.¹ Sample size determination has become more scientific by applying statistical power analyses. However, the choice of the effect size that is used in power analyses tends to be overly optimistic, often based on imprecise estimates from pilot data, and that can result in a negative trial. Methods to control false positive rates have changed over the past fifty years, yet the most effective strategy is to identify one primary outcome measure. It has become well known that a credible control must account for the passage of time, increased attention and expectation of therapeutic intervention.² Nevertheless, waitlist controls are used in studies of interventions for disorders such as post traumatic stress disorder (PTSD).^{3,4} The question of whether the developments in RCT design and analysis have had an impact on rates of regulatory approval of psychotropic medications will be discussed.

Learning Objectives:

- Consider developments in RCT design and analysis during the past half century
- Examine the implementation of these developments in trials for psychotropics
- Examine the impact of developments in methodology on regulatory approval of psychotropic medications

Literature References:

1. Hedeker D, et al. Longitudinal data analysis. Hoboken, NJ: John Wiley and Sons; 2006.
2. Klerman GL. Scientific and ethical considerations in the use of placebo controls in clinical trials in psychopharmacology. *Psychopharmacol Bull* 1986;22:25–29.
3. Leon AC, et al. Enhancing clinical trial design of interventions for posttraumatic stress disorder. *J Trauma Stress* 2009;22(6):603–11.
4. Institute of Medicine. Treatment of PTSD: an assessment of the evidence. Washington, DC: National Academies Press; 2008.

Adapting Trial Methodology for the Discovery of Novel and Personalized Medicines**George M. Garibaldi, M.D.**

Hoffmann-La Roche Pharmaceuticals

Use of current “state of the art” methodology and clinical outcomes will unlikely lead to the discovery of innovative therapeutics for the management of psychiatric disorders. The current approach is to identify populations that are likely to benefit from a novel therapy. Patients participating in clinical trials and meeting the same diagnostic criteria present a large heterogeneity of their clinical presentation. Another issue is that treatment success is determined based on the effect on rating scales that are accepted by clinicians and regulators, but have limited value to patients and payors.

Clustering analyses are used to identify homogeneous patient subpopulations within a given diagnostic entity. These patient phenotypes are characterized by the prominence of different symptom subsets. The appropriate patient phenotype can be selected to evaluate the effect of a novel therapeutic agent based on its pharmacologic profile.

Another important element for the development of innovative and personalized medicines is the creation and validation of novel clinical outcomes to better answer questions that matter for patients and policy makers. The “Patient Reported Most Troubling Symptoms” is a tailored approach to understand the effect of a therapeutic agent on disease features that matter to patients. Similar approaches are in development to evaluate the impact of therapeutic agents on disease aspects with a significant impact on the society.

A clustering symptom analysis was conducted on multiple clinical databases of patients with schizophrenia. Patients with predominant negative symptoms represented almost a third of the total population. The main characteristic of this patient population is their poor overall functioning compared with other patients with a similar DSM diagnosis. A recently completed study enrolled patients with symptom patterns consistent with the described patient phenotype. The main observation from this study was the high cross sectional and longitudinal correlation between the severity of negative symptoms and overall functioning. Additional findings from this study will be presented during the symposium.

Learning Objectives:

- Explore alternative outcomes to rating scales
- Review the possibility of alternative outcome measures, e.g., neuroimaging

Literature References:

None.

Workshop 3

Methodological Issues for Studying Negative Symptoms of Schizophrenia

9:00 a.m. – 12:00 p.m.

Workshop Overview

Stephen R. Marder, M.D.

University of California, Los Angeles School of Medicine

David G. Daniel, M.D.

United BioSource Corporation

Negative symptoms are common features of schizophrenia that usually persist despite antipsychotic treatment and significantly impair function and quality of life. There are numerous unresolved methodological issues in the design of clinical trials to study new treatments for negative symptoms. Attendees are invited to participate in consensus development with respect to several of the most salient issues:

- (1) Design issues in studies of broad spectrum and adjunctive agents. Among the topics of this presentation will be control agents, duration of trials and whether a functional co-primary is necessary;
- (2) Patient selection issues in negative symptom trials. Among the topics of this talk are the severity, persistence and span of negative and other symptoms;
- (3) Cognitive impairment and measurement of negative symptoms. Among the topics of this presentation will be the delineation of negative symptoms and cognition and the impact on study design; and
- (4) Issues in the selection of instruments for measuring negative symptoms. Among the topics of this presentation will be comparative psychometric qualities, clinical trial performance, and training experience with commonly used instruments for measuring negative symptoms in clinical trials.

Learning Objectives:

- Increase knowledge of issues in the design of clinical trials to study treatments of negative symptoms
- Increase understanding of issues in the delineation of measurement of cognitive domains and negative symptoms of schizophrenia
- Broaden awareness of issues in the selection of instruments to measure negative symptoms in clinical trials
- Become more aware of salient regulatory issues in clinical trials of agents to treat negative symptoms

Design Issues in Studies of Broad Spectrum and Adjunctive Agents for Negative Symptoms

Stephen R. Marder, M.D.

University of California, Los Angeles School of Medicine

This report will discuss issues in trial design that are important for studies of pharmacological agents for negative symptoms in schizophrenia. These issues are relatively straight forward for agents that would be added to an antipsychotic drug. For these trials, the guidelines that have been developed for cognition in schizophrenia are similar. Subjects would be stabilized on an antipsychotic and the comparison would be between adding the experimental agent or a placebo to the patient's antipsychotic. Study durations of 12–26 weeks have been proposed for these trials. Since negative symptoms are viewed as being related to outcome, it is unlikely that a co-primary measure of functional capacity would be needed. Alternatives for studies of agents that are broad spectrum—that is, drugs that are effective for psychotic and negative symptoms—will be discussed.

Learning Objectives:

- Inform the audience of issues that are relevant for the design of adjunctive drugs for negative symptoms
- Inform the audience about alternative study designs for trials of agents that treat psychotic and negative symptoms

Literature References:

- Kirkpatrick B, et al. The NIMH-MATRICES consensus statement on negative symptoms. *Schiz Bull* 2006;32(2):214–9.
- Buchanan RW, et al. A summary of the FDA-NIMH-MATRICES workshop on clinical trial design for neurocognitive drugs for schizophrenia. *Schiz Bull* 2005;31(1):5–19.

Workshop 3

Methodological Issues for Studying Negative Symptoms of Schizophrenia

9:00 a.m. – 12:00 p.m.

Patient Selection Issues in Negative Symptom Trials**Larry D. Alphas, M.D., Ph.D.**

Ortho-McNeil Janssen Scientific Affairs, LLC

Identifying the appropriate subjects for studies designed to find effective treatments for negative symptoms of schizophrenia is a challenging, but critical aspect of study design. Patient selection criteria are driven by the precise question being addressed by the study, but a key consideration for most studies is to demonstrate the specificity of the subject's negative symptoms and differentiating them from possible confounding conditions. Suggestions will be made for selection criteria that identify relevant populations as well as considerations for how these criteria might be adjusted to meet particular needs. Other considerations for patient selection that will be considered include the severity of negative symptoms, and their persistence. Following a brief presentation, the discussion will be opened to the audience for additional input.

Learning Objectives:

- Identify drivers of patient selection in negative symptom trials
- Develop specific selection criteria based on these identified drivers of patient selection

Literature References:

- Alphas L. An industry perspective on the NIMH consensus statement on negative symptoms. *Schiz Bull* 2006;32:225–30.
- Kirkpatrick B, et al. The NIMH-MATRICES consensus statement on negative symptoms. *Schiz Bull* 2006;32:214–19.

Cognitive Impairment and Measurement of Negative Symptoms**Richard S.E. Keefe, Ph.D.**

Duke University Medical Center

The relationship between cognitive impairment and negative symptoms in schizophrenia has repeatedly been demonstrated as modest. Pearson correlations of negative symptoms with general cognitive ability and most cognitive domains hover around $r=0.30$ in chronic samples (e.g., the Clinical Antipsychotic Trials of Intervention Effectiveness Study [CATIE]). While a relationship with negative symptoms was not a specific criterion for evaluating the tests included in the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB), their validity was determined in part by their relationship to social and occupational functioning and independent living. The arrow of causality between cognitive impairment and negative symptoms could reasonably run in either direction, but there is little empirical support that either symptom domain is primary. Antipsychotic treatments have had minimal effect on either of these two symptom domains in schizophrenia and first episode psychosis, and thus there have been limited opportunities to examine how efficacious treatment in one symptom domain may effect the other. The National Institute of Mental Health (NIMH) MATRICS project forwarded trial designs for assessing the effect of treatment on cognitive impairment in schizophrenia. Initially, a negative symptom rating greater than moderate was recommended as an exclusion criterion; however, that criterion was dropped in the NIMH Treatment Units for Research on Neurocognition and Schizophrenia (TURN) trials and a recent MATRICS Update publication. Thus, it raises the possibility that a treatment for cognitive impairment or negative symptoms could benefit each of these two aspects of schizophrenia simultaneously. This presentation will discuss the potential importance of cognitive change in the context of a negative symptom trial.

Learning Objectives:

- Develop an awareness of the relationship between cognitive impairment and negative symptoms
- Become cognizant of the effects of treatment on cognition and negative symptoms
- Understand the potential impact of cognitive change in the course of a negative symptom trial

Literature References:

- Keefe RSE, et al. Baseline neurocognitive deficits in the CATIE schizophrenia trial. *Neuropsychopharmacol* 2006;31:2033–46.
- Nuechterlein KH, et al. The MATRICS consensus cognitive battery: part 1. Test selection, reliability, and validity. *Am J Psychiatry* 2008;165:203–13.
- Lipkovich IA, et al. Relationships among neurocognition, symptoms and functioning in patients with schizophrenia: a path-analytic approach for associations at baseline and following 24 weeks of antipsychotic drug therapy. *BMC Psychiatry* 2009;9:44.

Workshop 3

Methodological Issues for Studying Negative Symptoms of Schizophrenia

9:00 a.m. – 12:00 p.m.

Issues in the Selection of Instruments for Measuring Negative Symptoms

David G. Daniel, M.D.
United BioSource Corporation

Selection of instruments for measurement of negative symptoms in clinical trials is an essential part of study design. The Scale for the Assessment of Negative Symptoms (SANS), the Negative Symptom Assessment Scale (NSA-16) and subscales from the Positive and Negative Symptoms Scale (PANSS) are reliable and valid measures of negative symptoms for clinical trials. However, they vary with respect to their psychometric qualities, the domains of negative symptoms addressed, inclusion of global assessments and amenability to obtaining agreement in scoring among investigators. The presentation and discussion will focus on the contrasting features of each of the above scales, the additional potential utility of global measures of negative symptoms and defining clinically meaningful effects.

Learning Objectives:

- Become aware of the contrasting features of the most commonly used scales for measurement of negative symptoms
- Become aware of the potential usefulness of global measures in assessing negative symptoms

Literature References:

Blanchard JJ, et al. The structure of negative symptoms within schizophrenia: implications for assessment. *Schiz Bull* 2006;32(2): 238–45.
Kirkpatrick B, et al. Assessing the efficacy of treatments for the deficit syndrome of schizophrenia. *Neuropsychopharmacol* 2000;22:303–10.

Food and Drug Administration (FDA) Perspective on Negative Symptoms as a Treatment Target

Robert L. Levin, M.D.
Food and Drug Administration

Negative symptoms of schizophrenia are not adequately addressed by available treatments for schizophrenia.¹ Thus, it is reasonable to consider them as a target for a treatment claim. We will discuss the issues that the Food and Drug Administration (FDA) has weighed in considering negative symptoms of schizophrenia as a novel and distinct drug target.² We will also identify a number of clinical trial design issues that the FDA views as important in deciding how best to conduct studies for this indication. These design issues include:

- (a) what population to study;
- (b) what phase of illness to target;
- (c) whether to focus on the negative symptom domain overall or on some specific aspect of negative symptoms;
- (d) optimal designs for adjunctive therapy and/or monotherapy (broad-spectrum agent) trials;
- (e) the role of functional measures in negative symptom trials; and
- (f) the importance of characterizing the relationship between negative symptoms and cognitive impairment of schizophrenia.

Learning Objectives:

- Increase knowledge of issues that FDA considers important regarding negative symptoms as a treatment indication
- Increase understanding of potential study designs for assessing negative symptoms
- Broaden their awareness of the progress, challenges, and remaining questions regarding approaches to studying negative symptoms in definitive trials

Literature References:

1. Kirkpatrick B, et al. The NIMH-MATRICES consensus statement on negative symptoms. *Schiz Bull* 2006;32:214–9.
2. Laughren T, et al. Food and drug administration perspective on negative symptoms in schizophrenia as a target for a drug treatment claim. *Schiz Bull* 2006;32:220–2.

Workshop 4

Evaluating New Treatments for Co-Occurring Mental Health and Substance Abuse Disorders: Design Issues and Clinical Implications

1:30 p.m. – 4:30 p.m.

Workshop Overview

Barbara J. Mason, Ph.D.
Scripps Research Institute

Jack D. Blaine, M.D.
National Institute on Drug Abuse (Contractor)

Objective: The objective of this workshop is to convey state-of-the-art information about designing randomized controlled trials (RCTs) to evaluate new treatments for individuals with co-occurring mental health and substance use disorders, and the implications of such study designs for clinical practice.

Background: The presence of a substance use disorder increases the risk of a concurrent independent anxiety disorder 2-fold, major depression 2.5-fold and mania 4-fold. Furthermore, subsyndromal mood symptoms and sleep disturbance have been identified as common precipitants of return to substance use, but have historically not been the focus of treatment research. Recently, the link between attention deficit hyperactivity disorder (ADHD) and substance abuse has been highlighted, suggesting a need for treatment research with a developmental focus on adolescence.

Methods: The first presentation will present STAR*D data on whether comorbid substance abuse disorder impair recovery from major depression with SSRI treatment. The second presentation will focus on the use of gabapentin in the treatment of subsyndromal disturbances in mood in alcohol dependence. The next presentation will address the RCT evidence base and treatment research challenges specific to bipolar disorder and comorbid substance abuse, including substances that mask or exacerbate bipolar symptoms, medication noncompliance, and identification of early warning signs and strategies to prevent clinical deterioration. Next, a RTC of adolescents with ADHD and comorbid substance abuse will be presented, and the potential effects of concomitant behavioral treatments on medication RCTs, e.g., enhanced placebo response versus ethical considerations of placebo alone, will be discussed. The final presentation will address the complex etiologic relationship between anxiety and substance use disorders and how each may modify the presentation and course of the other as well as require consideration of a medication's potential for abuse or toxicity when combined with the abused substance.

Learning Objectives:

- Learn diagnostic issues specific to individuals with co-occurring mental health and substance use disorders, e.g., symptoms of one disorder being masked or exacerbated by the co-occurring disorder
- Become familiar with treatment considerations specific to individuals with co-occurring mental health and substance use disorders, e.g., abuse potential and alcohol/drug interactions involving prescribed medications

Does Comorbid Substance Use Disorder Impair Recovery from Major Depression with Selective Serotonin Reuptake Inhibitor (SSRI) Treatment? An Analysis of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Level One Treatment Outcomes

Lori L. Davis, M.D.
Tuscaloosa Veterans Affairs Medical Center

Many patients with major depressive disorder (MDD) present with concurrent substance use disorders (SUDs), which has been thought to impair their response to antidepressants. Clinicians often delay antidepressant treatment until sustained sobriety has been established. Unfortunately, these comorbid subjects are typically excluded from depression treatment trials, leaving a gap in understanding the treatment outcomes. In the STAR*D study, 2,876 adult outpatients diagnosed with nonpsychotic MDD were prospectively treated with the SSRI citalopram, and returned for at least one post-baseline visit. Participants with SUD (29%) and without SUD (71%) were compared in regard to baseline clinical and sociodemographic features and treatment response. The group with MDD and SUD was further subdivided into those with alcohol only, drug only, and both alcohol and drug use. Despite clear sociodemographic and clinical differences, there were no significant differences between groups in the time to achieve response or rates of response to citalopram; however, those who endorsed both alcohol and drug use had significantly reduced rates of remission and significantly increased times to reach remission compared to the MDD group without SUD. In addition, subjects with MDD and SUD had higher risk of psychiatric serious adverse events (3.3% versus 1.5%) and hospitalization (2.8% versus 1.2%). The results indicate that first-line treatment with citalopram in depressed patients with alcohol or drug use respond as well as those without SUD. More intensive treatment is most likely needed for MDD patients with both drug and alcohol use disorders.

Learning Objectives:

- Understand the differences in baseline characteristics of persons with major depression and concurrent substance use disorders
- Understand the differences in outcome to citalopram treatment between persons with MDD with or without concurrent substance use disorders

Literature References:

- Davis LL, et al. Are depressed outpatients with and without a family history of substance use disorder different? a baseline analysis of the STAR*D cohort. *J Clin Psych* 2007;68:12:1931-38.
- Davis LL, et al. Substance use disorder comorbidity in major depressive disorder: a confirmatory analysis of the STAR*D cohort. *Am J Addict* 2006;15:178-285.

Workshop 4

Evaluating New Treatments for Co-Occurring Mental Health and Substance Abuse Disorders:
Design Issues and Clinical Implications

1:30 p.m. – 4:30 p.m.

Gabapentin Treatment of Subsyndromal Disturbances in Mood in Alcohol Dependence

Barbara J. Mason, Ph.D.
Scripps Research Institute

Background: Subsyndromal disturbances in mood have been identified as predictors of relapse to drinking, but these symptoms have not been the focus of pharmacotherapies in alcohol dependence.

Hypothesis: We hypothesized that gabapentin, a GABAergic modulator, would decrease drinking and mood disturbances in recently abstinent alcoholics significantly more than placebo.

Methods: Outpatients with current DSM-IV alcohol dependence and no other major psychiatric disorders were randomized to 12 weeks of double-blind treatment with 0, 900, or 1800 mg/day of gabapentin and weekly counseling.

Results: Subjects were 150 alcoholics (55.3% males, mean age of 43.99 (+/- 11) years). Significant linear dose effects were found for gabapentin to decrease drinking, Beck Depression Inventory scores, and Pittsburgh Sleep Quality scores relative to placebo. There were no serious drug-related adverse events and significantly more gabapentin than placebo-treated subjects indicated a wish to continue treatment and felt treatment was helpful with their symptoms.

Conclusions: These data lend support to gabapentin treatment of subsyndromal disturbances in mood and prevention of relapse in recently abstinent patients with alcohol dependence.

Learning Objectives:

- Identify symptoms of protracted abstinence in substance dependence
- Understand the rationale for a neuromodulatory approach to treatment of substance dependence

Literature References:

Mason BJ, et al. Proof-of-concept human laboratory study for protracted abstinence in alcohol dependence: effects of gabapentin. *Addict Biol* 2009;14:73–83.
Lowman C, et al. Replication and extension of Marlatt's taxonomy of relapse precipitants: overview of procedures and results. The Relapse Research Group. *Addiction* 1996;91:S51–S71.

Conceptual and Methodological Issues in Clinical Trials of Comorbid Bipolar and Alcohol Use Disorders

Ihsan M. Salloum, M.D., M.P.H.
University of Miami Miller School of Medicine

Comorbidity of bipolar-alcohol use disorders is highly prevalent and is associated with significant negative consequences and unmet treatment needs. The clinical complexity presented by this comorbidity is a major challenge to clinical practice and to conducting clinical trials. This presentation will review experience gained from published and recently completed pharmacotherapy and psychotherapy trials in this population including placebo-controlled studies with anticonvulsants, atypical antipsychotics and combined medication studies as well as studies of novel integrated psychotherapies. This presentation will also focus on key conceptual and methodological issues involving the design and conduct of clinical trials in this population, including study design, population selection, recruitment and retention, psychosocial platform, outcome measures, safety and ethical issues involved. It will also discuss implications of current findings for clinical care and for future directions in research.

Learning Objectives:

- Learn about the results of the latest pharmacotherapy and psychotherapy trials in comorbid alcoholism and bipolar disorder
- Understand key methodological challenges in conducting clinical trials for this complex population

Literature References:

Salloum IM, et al. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: a double-blind placebo-controlled study. *Arch Gen Psychiatry* 2005;62(1):37–45.
Brown ES, et al. A randomized, double-blind, placebo-controlled add-on trial of quetiapine in outpatients with bipolar disorder and alcohol use disorders. *J Clin Psychiatry* 2008;69(5):701–5.

Workshop 4

Evaluating New Treatments for Co-Occurring Mental Health and Substance Abuse Disorders: Design Issues and Clinical Implications

1:30 p.m. – 4:30 p.m.

Research Advances in the Treatment of Adolescents with Co-Occurring Attention Deficit Hyperactivity Disorder (ADHD) and Substance Use Disorders: Implications for Clinical Practice and Study Design

Paula D. Riggs, M.D.
University of Colorado, Denver

Background: 30–50% of adolescents referred for treatment of substance use disorders (SUD) have co-occurring attention deficit hyperactivity disorder (ADHD), which is associated with poorer treatment outcomes. However there has been a lack of research evaluating the impact of combined pharmacotherapy and behavioral interventions for co-occurring ADHD and SUD in dually-diagnosed youth. Results of the first multi-site randomized controlled trial of Osmotic Release Oral System extended release Methylphenidate (OROS-MPH) versus placebo in adolescents concurrently enrolled in outpatient substance abuse treatment will be reported.

Methods: 303 adolescents (ages 13–18) with DSM-IV ADHD and SUD were randomly assigned to 16 weeks of OROS-MPH or placebo. All participants concurrently received weekly individual cognitive behavioral therapy (CBT) targeting substance abuse.

Results: There was a clinically and statistically significant decrease in ADHD symptoms in both treatment groups (45%, $p < 0.0001$) but no difference between groups based on adolescent DSM-IV ADHD symptom checklist scores. Parent ratings of ADHD symptoms and severity were lower in adolescents treated with OROS-MPH compared to placebo at 8 ($p < 0.0025$) and 16 weeks ($p < 0.0015$). Significant improvement in problem-solving ability ($p < 0.0023$) and focused coping skills ($p < 0.003$) were reported by adolescents treated with OROS-MPH+CBT but not placebo+CBT. Past 28 days drug use decreased significantly in the OROS-MPH+CBT (-6.1 days; 43%) and placebo+CBT (-4.9 days; 33%) treatment groups but was not statistically different between groups. However, subjects treated with OROS-MPH had more negative urine drug screens (3.8) compared to placebo + CBT (2.8; $p = 0.045$).

Conclusions: OROS-MPH was safe and well-tolerated despite non-abstinence in most subjects. Results support some “added value” of OROS-MPH over placebo for ADHD. However, greater than expected decrease in ADHD symptoms in both groups suggests that CBT may have contributed to both ADHD and substance outcomes.

Learning Objectives:

- Learn about results of a multi-site randomized trial of OROS-MPH + CBT in adolescents with co-occurring ADHD and SUD
- Learn the implications of study results for clinical practice and the design of future trials of combined pharmacotherapy and behavioral interventions
- Learn the broader context of comorbidity treatment research in adolescents as background for interpreting data presented from the multisite trial

Literature References:

- Riggs PD, et al. Co-morbid psychiatric and substance abuse disorders: recent treatment research. *Substance Abuse* 2008;29(3):51–63.
- Riggs PD, et al. A randomized controlled trial of fluoxetine and cognitive behavioral therapy in adolescents with major depression, behavior problems, and substance use disorders. *Arch Pediatr Adolesc Med* 2007;161(11):1026–34.

Post Traumatic Stress Disorder (PTSD) and Substance Use Disorders (SUDs)

R. Bruce Lydiard, M.D., Ph.D.
Ralph H. Johnson Veterans Affairs

The relationship between post traumatic stress disorder (PTSD) and substance use disorders (SUDs) is complex. A number of epidemiologic studies demonstrate that PTSD and SUDs co-occur more commonly than would be expected by chance and that the odds ratio of having a SUD for an individual with PTSD is in the range of 4.0–5.0. Studies also indicate that a high percentage (25–60%) of individuals seeking treatment for SUDs have lifetime PTSD. There are a number of potential etiologic connections between SUD and PTSD. Studies exploring the etiologic connection between these disorders will be reviewed including some focused on self-medication of PTSD symptoms by drugs of abuse, studies focused on exacerbation of PTSD symptoms by drugs of abuse and studies exploring common neurobiology across disorders. The implications for treatment of various etiologic connections between PTSD and SUDs will be discussed.

Learning Objectives:

- Learn about the prevalence of co-occurring PTSD and substance use disorders
- Learn about treatment options for PTSD and co-occurring substance use disorders
- Learn about the neurobiologic connections between PTSD and SUDs

Literature References:

- Kessler RC, et al. Posttraumatic stress disorder in the national comorbidity survey. *Arch Gen Psychiatry* 1995;52(12):1048–60.
- Jacobsen LK, et al. Substance use disorders in patients with posttraumatic stress disorder: a review of the literature. *Am J Psychiatry* 2001;158(8):1184–90.
- Back SE, et al. Symptom improvement in co-occurring PTSD and alcohol dependence. *J Nerv Ment Dis* 2006;194(9):690–96.

Workshop 5

Winning Strategies for Securing NIMH Funding

1:30 p.m. – 4:30 p.m.

Workshop Overview

Tracy L. Waldeck, Ph.D.

National Institute of Mental Health

With the changing landscape of National Institutes of Health (NIH) research funding, prospective investigators may be seeking new tools to aid in developing a successful grant application. This session is designed to aid investigators in navigating the many changes that have taken place in the past few years in how NIH receives, reviews and funds grant applications.

This workshop discussion with National Institute of Mental Health (NIMH) staff promises to explain effective techniques for transforming research questions into competitive applications and for presenting your ideas to reviewers and the Institute. In addition, an overview of the NIH process from submission to award will be presented. Learn tips on how to find the Institute's areas of high priority research and topics already funded by the Institute.

The workshop will also provide in-depth explanation of the changes to the structure and review of grant applications occurring over the past two years. Finally, substantial question and answer time with NIMH review, program and policy staff where you can obtain information 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 how to turn a great idea into a successful application and how to respond to a summary statement
- Learn about the recent changes to the NIH application and peer review process

Identifying Relevant Staff and NIMH Research Priorities

Joel T. Sherill, Ph.D.

National Institute of Mental Health

Is My Idea SF 424 Worthy?

Michael J. Kozak, Ph.D.

National Institute of Mental Health

Your Application in the New Format

David M. Armstrong, Ph.D.

National Institute of Mental Health

Issues and Challenges in Peer Review

David I. Sommers, Ph.D.

National Institute of Mental Health

Impact versus Significance

David W. Miller, Ph.D.

National Institute of Mental Health

Overall Impact/Priority Score=27: What Now?

Christopher S. Sarampote, Ph.D.

National Institute of Mental Health

Late-Breaking News from NIMH

Tracy L. Waldeck, Ph.D.

National Institute of Mental Health

Questions and Answers with One-on-One Time with National Institute of Mental Health Staff

This interactive discussion panel is designed to provide prospective investigators with an overview of the National Institute of Mental Health (NIMH) grant funding process, from idea generation to submission and review to payment. Topics will be presented by representatives from NIMH programmatic, review, and extramural policy staff and include the sources of funding information available to applicants and the process by which applications are developed, electronically submitted and referred for review. Specific information will be provided on the recent significant changes to National Institutes of Health (NIH) submission and review system, what applicants and reviewers need to know in order to best prepare applications for review, as well as recommendations as to how applicants can make the best use of feedback from review. There will be ample time for questions and answers during the session and the panel members will be able to answer questions related to any aspect of the application process.

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 how to turn a great idea into a successful application and how to respond to a summary statement.
- Learn about the recent changes to the NIH application and peer review process.

Workshop 6

**The NIMH Bipolar Trials Network Lithium Treatment Moderate Dose Use Study (LiTMUS):
A Randomized Comparative Effectiveness Trial of Adjunctive Lithium in Bipolar Disorder**
1:30 p.m. – 4:30 p.m.

Workshop Overview**Michael E. Thase, M.D.**

University of Pennsylvania School of Medicine

Lithium as monotherapy is used infrequently; combination therapy regimens predominate for all clinical states of bipolar disorder. There is a public health need to assess the effectiveness of lithium added to flexible medication regimens of other established drugs for acute and continuation treatment for bipolar disorder. This comparative effectiveness study, conducted by the six centers comprising the Bipolar Trials Network, addressed the question do well-tolerated doses of lithium (Li) combined with guideline-based optimized pharmacological treatment (OPT) improve outcomes and decrease the need for medication changes over six months of follow-up? The Li+OPT group received lithium combined with OPT, the control group received OPT that excluded lithium. OPT included at least one medication Food and Drug Administration (FDA)-approved for the treatment of bipolar disorder. OPT was allowed to change in both groups over the course of the six-month study, based on clinical needs of the participants and consistent with the goal of helping participants achieve sustained remission with minimal adverse effects. Outcomes were assessed by raters blind to randomization status. Statistical techniques for longitudinal studies, which are capable of dealing with the shifting clinical states and tolerability issues in patients with bipolar disorders, can support better informed choice and application of regimens. Methodological contributors to the robust enrollment and uncommonly high full trial retention rate, and key results for the Lithium Treatment – Moderate Dose Use Study (LiTMUS) will be discussed.

Learning Objectives:

- Be better equipped to conduct randomized, pragmatic intervention trials with ecological validity in bipolar disorders
- Be capable of assessing the strengths and limitations of alternative design methodologies and statistical procedures that are available for bipolar intervention studies
- Update the utility of adjunctive, tolerably dosed lithium with results from a study with unique methodologies relevant to current treatment practices in bipolar disorder

**Methodologies to Retain Subjects to Study Completion,
Thereby Providing More Valid Information on
Comparative Effectiveness of Treatments**

Charles L. Bowden, M.D.

University of Texas Health Science Center, San Antonio

The Lithium Treatment – Moderate Dose Use Study (LiTMUS) enrolled 107% of the planned sample within the planned enrollment period and had an all-cause discontinuation rate below 15%. The methodological initiatives that contributed to this high full trial completion rate, an essential component for generation of valid comparative effectiveness information, included the following a priori actions. The trial was incorporated into environments of sustained, excellent expert clinical care. The adjunctive, open (with a single-blind rater) randomized design was understandable to all screened patients; conformed to patients' expectations of high quality clinical care; and facilitated clinicians providing optimized care, as they were aware of whether or not lithium was being used in individual patients. Patients recognized the importance of the rationale for the study; establishing pragmatic, research-based guidelines for the role and use of lithium in bipolar disorder, including the intent to provide adequately tolerated regimen. We incorporated provisions to continue treatment even if lithium was discontinued (due to tolerability or adherence problems), planned scale administration and subject time at visits to minimize time burden and adequately compensated patients for their efforts. Our impressions from meetings with stakeholder groups and comments by participants are that substantially fewer potential participants were interested in similar studies with one to two year duration.

Learning Objectives:

- Develop familiarity with methods which yielded retention rates above 85% for the six-month randomized LiTMUS study in bipolar disorder
- Recognize and have a workable plan for incorporating prospective randomized research into a longitudinal program of related illness care
- Develop approaches that retain subjects beyond development of a relapse or new episode

Literature References:

- Sachs GS, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med* 2007;356:1711–22.
- Van der loos M, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009;70:223–31.
- Bowden C, et al. A 12-week, open, randomized trial comparing sodium valproate to lithium in patients with bipolar I disorder suffering from a manic episode. *Int Clin Psychopharmacol* 2008;23(5):254–62.

Workshop 6

The NIMH Bipolar Trials Network Lithium Treatment Moderate Dose Use Study (LiTMUS): A Randomized Comparative Effectiveness Trial of Adjunctive Lithium in Bipolar Disorder

1:30 p.m. – 4:30 p.m.

Sample Selection and Inclusion Criteria for Generalizability in Comparative Effectiveness Studies of Bipolar Disorder

Joseph R. Calabrese, M.D.

Case Western Reserve University School of Medicine

Knowledge of treatment response and characteristics of bipolar disorder is shaped by the samples recruited into treatment trials. "Real world" clinical populations are not routinely included in efficacy research, as samples for randomized controlled trials conducted for regulatory approval routinely exclude patients with comorbidities, complex presentations and high illness severity. Moreover, such studies also commonly assess interventions (such as monotherapy or a very few two-drug therapies) that are substantially less complex and heterogeneous than those encountered in clinical practice. LiTMUS is a comparative effectiveness trial that addressed this efficacy-effectiveness gap in bipolar disorder therapeutics by recruiting patients with heterogeneous clinical presentations (bipolar or bipolar II disorder with at least moderate mood elevation or depression symptoms, and commonly with comorbid psychiatric and medical disorders) and diverse current medications, from ethnically, socioeconomically and geographically diverse settings. The principle illness severity inclusion criterion in LiTMUS was that subjects be currently at least moderately symptomatic, defined as having a Clinical Global Impressions Scale for Bipolar Disorder (CGI-BP) Overall Severity score of greater than or equal to 3. The illness history, presenting severity, clinical states and functional status of the sample will be presented. The bottom line from these results is that the straightforward CGI-BP Overall Severity entry criterion yielded a sample noteworthy for high illness severity, ecological validity and generalizability to community efforts to treat bipolar disorder.

Learning Objectives:

- Be better equipped to understand the magnitude of the decreased generalizability associated with the exclusion criteria typically associated with efficacy studies as compared to pragmatic effectiveness trials such as those employed in the LiTMUS effectiveness trial
- Be capable of assessing the strengths and limitations of the inclusion and exclusion criteria employed in the LiTMUS effectiveness trial and the extent to which these criteria resulted in improved generalizability

Literature References:

- Merikangas KR, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. *Arch Gen Psychiatry* 2007 May 1;64(5):543–52.
- Kessler RC, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry* 2005;62(6):617–27.

Developing a Novel Outcome Measure of Comparative Effectiveness: Necessary Clinical Adjustments (NCAs)

Andrew C. Leon, Ph.D.

Weill Medical College of Cornell University

The Bipolar Trials Network (BTN) investigators decided to include an innovative co-primary outcome measure in addition to using a standard primary outcome of illness severity as assessed by the Clinical Global Impressions Scale for Bipolar Disorder (CGI-BP) Overall Severity score. NCAs represent a tally of modifications of all medications used to treat psychiatric disorders or side effects, including dose changes, which are triggered in response to a patient's symptom severity, inadequate function or side effects. More specifically, NCAs consist of all adjustments in medications that are classified as necessary to respond to clinical need, e.g., exacerbation of mood symptoms, emergence of a mood episode, persistence of symptoms or adjustments because of adverse events. In contrast, NCAs do not include decreases in doses based on positive responses or a clinician's judgment that a medication is no longer required. NCAs do not directly influence subsequent changes in treatment. Yet, total NCAs does serve as a proxy for overall effectiveness of a treatment regimen. A further reason for including an innovative co-primary outcome is based upon the comparative effectiveness aspect of the design, which is meant to reflect physicians' prescribing behavior in clinical practice. That is, study clinicians will be instructed to render treatment as aggressively as necessary to optimally control participant's symptoms and minimize adverse effects.

Limitations of the NCA metric include its novelty, which initially may be met with skepticism by the field, and its operational challenges. Importantly, we propose to assess relationships between NCAs and conventional mood and quality of life outcomes.

Learning Objectives:

- Better understand the rationale for the development of a new outcome measure: Necessary Clinical Adjustments
- Better understand the implementation of Necessary Clinical Adjustments

Literature References:

- Nierenberg AA, et al. ME Lithium treatment—moderate dose use study (LiTMUS) for bipolar disorder: rationale and design. *Clin Trials*. Forthcoming.
- Leon AC, et al. Enhancing clinical trial design of interventions for posttraumatic stress disorder. *J Trauma Stress*. Forthcoming

Workshop 6

**The NIMH Bipolar Trials Network Lithium Treatment Moderate Dose Use Study (LiTMUS):
A Randomized Comparative Effectiveness Trial of Adjunctive Lithium in Bipolar Disorder**
1:30 p.m. – 4:30 p.m.

**Comparative Effectiveness Results of the LiTMUS Trial:
Hypotheses and Rationale**

Andrew A. Nierenberg, M.D.

Massachusetts General Hospital, Harvard Medical School

The final patient visit in Lithium Treatment – Moderate Dose Use Study (LiTMUS) occurred in February 2010. Data have been collated to facilitate prompt analyses of outcome. The primary hypothesis is that subjects randomized to lithium combined with optimized pharmacological treatment (Li+OPT) will exhibit greater improvement in mean Clinical Global Impressions Scale for Bipolar Disorder (CGI-BP) Overall Severity scores over the course of six months, compared to those receiving OPT without lithium. Mixed-effects linear regression analyses will compare the two intervention groups on the repeated assessments of the CGI-BP Overall Severity scores over the six month trial. A treatment by time interaction will be used to determine if the rate of reduction in illness severity varies between two intervention groups over the course of acute treatment. The co-primary hypothesis is that patients who are randomized to Li+OPT will require fewer Necessary Clinical Adjustments (NCAs) over the course of six months, compared to those prescribed OPT. This variable is a proxy for the clinical burden of an intervention and embodies treatment changes due to lack of efficacy and/or safety/tolerability issues (i.e., adverse events). This dependent variable will be expressed as NCAs per month. This monthly rate will be used to account for attrition and the resulting differential exposure time. We have posited four hypothesized moderators: family history of mood disorders (y/n), age of onset (<18 versus 18+), history of rapid cycling (y/n), and history of mixed states (y/n). It is hypothesized that there will be an enhanced benefit with adjunctive lithium for those with family history of mood disorders, a later (adult rather than pediatric) onset age, no history of rapid cycling, or no history of mixed states.

Learning Objectives:

- Be informed of the objectives of the LiTMUS trial regarding establishing current utility of lithium as component of treatment regimens for symptomatic bipolar disorder
- Become knowledgeable about the key characteristics of patients enrolled into LiTMUS, including illness severity, clinical state, functional status, prior treatment and illness course and demographic characteristics

Literature References:

- Nierenberg AA, et al. LiTMUS study group lithium treatment—moderate dose use study (LiTMUS) for bipolar disorder: rationale and design. *Clin Trials* 2009 Dec;6(6):637–48.
- Grunze H, et al. The World Federation of Societies of Biological Psychiatry guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. *World J Biol Psychiatr* 2009;10:85–116.



Plenary Session I

Learning from the Past to Advance the Future of Mental Health Treatment

10:00 a.m. – 12:00 p.m.

Overview

Nina R. Schooler, Ph.D.

State University of New York, Downstate Medical Center

This plenary session will highlight the scientific evolution and the lessons learned over the last 50 years of clinical trials in central nervous system (CNS) disorders and their implications for future development.

George Simpson will discuss the origins of ECDEU/NCDEU and the interaction between industry, academia and the Food and Drug Administration during the early evolution of research in clinical psychopharmacology and how the landscape, "rules" and opportunities have changed over time.

John Kane will review the evolution of clinical research in schizophrenia and how the NCDEU meeting has come to reflect the complex nature of clinical trials and the respective roles of the National Institute of Mental Health and academia in drug development and clinical trials.

Helena Kraemer will review what we have learned about doing randomized clinical trials and how this should influence future studies. She will discuss the role of good pilot studies, sampling, study design, outcome measures and data analysis as well as conceptual advances in the analysis of mediating and moderating variables and their role in achieving our goal of personalized medicine.

Husseini Manji will discuss the challenges facing the pharmaceutical industry and the methodological issues that need to be addressed in collaboration with academia. He will discuss why some large companies are backing away from research in psychopharmacology and focusing on neurodegenerative diseases at a time when enormous opportunities remain in advancing the treatment of psychiatric illness.

Learning Objectives:

- Recognize the role of ECDEU/NCDEU in advancing the science of medication development for psychiatric disorders
- Understand the changes and continuities in the contributions of academia, industry and the government (FDA and NIMH) to clinical trials in CNS disorders with schizophrenia as a specific example
- Learn about the current status of key methodological aspects of clinical trials including the role of pilot studies, the distinction between hypothesis testing and exploratory analyses and use of moderator and mediator analysis in advancing the goal of personalized medicine
- Learn about strategies within the pharmaceutical industry to advance treatment of CNS disorders in view of economic and other challenges



Panel I (Part I)

Perspectives of 50 Years of Brain Research and Drug Discovery

2:00 p.m. – 3:30 p.m.

Panel Overview

Donald S. Robinson, M.D.

Worldwide Drug Development

Karl E. Rickels, M.D.

University of Pennsylvania School of Medicine

The serendipitous discovery of chlorpromazine, monoamine oxidase inhibitors and tricyclic antidepressants in the 1950s heralded the modern era of psychopharmacology and brain research and presaged the birth of the New Clinical Drug Evaluation Units (NCDEU) branch of National Institute of Mental Health (formerly Early Clinical Drug Evaluation Units [ECDEU]). Fundamental advances in our knowledge of the neurosciences have resulted in major shifts in understanding and hypotheses of brain function and mental illnesses. Despite significant discoveries relating to brain, the pharmacologic mechanisms of action of psychotropic drugs, and diagnostic phenomenology, as well as more sophisticated methods of assessing clinical drug response, research efforts have been ineffectual, or at best, slow to yield therapeutic breakthroughs. Failures in psychotropic drug discovery and development efforts have been commonplace; improvements in clinical therapeutics have proven to be modest compared with the efficacy of agents existing at the time when NCDEU was set up by the NIMH to promote early assessment and rapid turnaround of new compounds.

The impact of 50 years of research in psychopharmacology and clinical therapeutics will be reviewed by a panel of scientific leaders and experienced investigators. The discoveries and investigative findings of greatest importance will be highlighted. Limitations of our current state of knowledge will be addressed and research deserving of future investigation identified for advancing the treatment of mental disorders.

Learning Objectives:

- Review key advances in psychopharmacology
- Identify future research directions

The Evolution of Psychopharmacology

Donald S. Robinson, M.D.

Worldwide Drug Development

The use of methylene blue dye, a phenothiazine derivative that selectively stains nervous tissue, was one of the first clinical trials in psychopharmacology with a scientific rationale.¹ The prophylactic effect of lithium salts, a health nostrum, had previously been noted in mania in the 1880s based on observations in patients. Several decades later, the importance of placebo-controlled trials in psychopharmacology was recognized in a study by Dub and Lurie in 1939 on the use of benzedrene for treating the depressed phase of the psychotic state. The modern era of psychopharmacology began in the 1950s with the concurrent and serendipitous discoveries of chlorpromazine, iproniazid and imipramine, resulting from astute clinical observation, not controlled trials. Early Clinical Drug Evaluation Units (ECDEU) evolved from a steering committee set up by Jonathan Cole in 1959 to standardize clinical research methodologies in psychopharmacology, resulting in the ECDEU Assessment Manual,² which became a bible of the field. A milestone study reported by Klein and Fink at an early ECDEU meeting was a blinded trial of imipramine, chlorpromazine and placebo at Hillside Hospital, which enrolled psychiatric patients without regard for diagnosis.¹

The panel will highlight significant advances since that era in psychopharmacology and our understanding of the mechanisms of action of psychotropic agents. Gaps in knowledge and future avenues for research will be presented.

Learning Objectives:

- Be familiar with the history of drug discovery in psychopharmacology
- Understand of the role of empirical research in drug development

Literature References:

1. Healy D. The creation of psychopharmacology. Cambridge, MA: Harvard University Press; 2004.
2. Guy W, editor. ECDEU Assessment Manual. Rockville, MD: U.S. Dept of Health, Education, and Welfare; 1976.

Panel I (Part I)

Perspectives of 50 Years of Brain Research and Drug Discovery

2:00 p.m. – 3:30 p.m.

From ECDEU to NCDEU: 50 Years on the Final Common Therapeutics Pathway

Jerome Levine, M.D.

Formerly Nathan S. Kline Institute for Psychiatric Research and New York University School of Medicine

In the 50-year period of the National Institute of Mental Health (NIMH) ECDEU and NCDEU programs (1960–2010), our knowledge of brain and mental function and dysfunction, and the tools available to study them, have changed and improved dramatically. However, no matter how novel or new the technique for postulating a new pharmacologic therapeutic agent it must still pass thru the rigors of clinical trial testing before becoming an accepted treatment for mental illness. And this is the area where ECDEU and NCDEU have played a pivotal role in modern psychopharmacology.

In 1960, there was no requirement that a drug have proof of efficacy before being marketed, and yet the modern era of psychotherapeutics (e.g., chlorpromazine and meprobamate) was well under way and a plethora of new drugs was coming to market. There was great doubt among the prominent and predominant psychiatrists of the day that drugs could be useful in treating mental disorders and, at the same time, there were very few clinical scientists and tools for testing (proving) efficacy. To their credit, Jonathan Cole and Gerald Klerman of the Psychopharmacology Service Center (PSC) of the NIMH, and their consultants, recognized this problem and suggested a grant supported research program be developed to create a number of centers that could clinically test the drugs being investigated and marketed for the treatment of mental illness.

This was done and over the period of 1960–1967, 20 centers located across the U.S. and in Canada and England and France conducted clinical trials of drugs of their choosing largely independent of industry funding and protocol guidance. During those years, investigators were called together by NIMH for closed annual or semi-annual meetings to present their results and methods of carrying out trials. In 1962, when the U.S. Congress passed amendments to the Food and Drug Administration (FDA) law requiring proof of efficacy before marketing these centers and the PSC became important to both industry and the FDA.

Standards for clinical trials in psychopharmacology were needed, and the ECDEU investigators with PSC staff agreed on a set of clinical rating instruments and forms that they would use in their studies. These were published as the ECDEU Assessment Manual. At the same time electronic data handling and computer technology became available and the PSC established a data facility at George Washington University that developed standard methods for collecting and analyzing data from the centers that were using forms from the Assessment Manual. Between 1967–1979, over 600 studies were analyzed, reported and stored in a clinical trials data bank. Because there were many more clinical psychopharmacology investigators who were carrying out clinical trials the Annual Meetings were opened to all investigators.

During this period, the number of drugs coming from industry that could be studied “early” was markedly reduced and to reflect this the name of the program was changed from Early Clinical Drug Evaluation (ECDEU) to New Clinical Drug Evaluation (NCDEU). Because the technique of clinical assessment was now established and disseminated, NIMH review committees came to believe that companies and not the federal government should support this clinical drug evaluation. In 1979, grant support for ECDEU ended. However, the annual meetings, where results of trials and new methods were presented and where there was a neutral forum where investigators, FDA and pharmaceutical industry come together, has continued as the NCDEU program of today.

Fundamental Advances in Neuropharmacology

Stephen M. Stahl, M.D., Ph.D.

University of California, San Diego School of Medicine

Early neuropharmacology is largely the story of serendipity, with biochemical targets for new drugs evolving only after the mechanisms were later discovered for agents already known to work clinically for depression, psychosis and anxiety. Clearly, much of the past 50 years of drug discovery in neuropharmacology is linked to the three monoamines serotonin, norepinephrine and dopamine, and to either blocking transporters for these neurotransmitters, or to actions at their various receptor subtypes.

Strategies have evolved from “dirty drugs” with multiple simultaneous neurochemical mechanisms, some therapeutic and some causing side effects, to “magic bullet” hyperselective agents, and now back again to “multifunctional” drugs with multiple simultaneous therapeutic mechanisms, again, mostly targeting one or more monoamine system.

Neurobiological advances that have aided this process include the discovery of monoamine pathways and topographical localization of neurotransmitter receptor subtypes. In recent years, this notion has evolved to topographical localization of function as well, with the increasingly feasible proposition of being able to image neuronal functioning in discrete pathways in living patients.

Attention is now turning to other neurotransmitter systems, especially glutamate, but also various neuropeptides as the localization and functioning of these systems are being clarified. In many ways, the “second generation” of antidepressants and antipsychotics of the 1990s are “fine tune” adjustments upon the originally discovered agents of the 1950s such as chlorpromazine and imipramine. Now what is needed as scientists are exhausting the same therapeutic targets, is a set of entirely new therapeutic targets with the potential for greater efficacy such as for more remission in depression, better stabilization of bipolar disorder without polypharmacy and for all phases of the illness, and for attaining true remission in schizophrenia, including especially cognitive and negative symptoms.

Learning Objectives:

- Review the neuropharmacologic basis of the original discoveries of psychotropic drugs in the era of the 1950s
- Compare this to the neurobiological strategy of drugs that have followed over the ensuing 50 years

Literature References:

- Stahl SM. Stahl’s essential psychopharmacology, 3rd ed. New York:Cambridge University Press; 2008.
- Stahl SM. Finding what you are not looking for: strategies for developing novel treatments in psychiatry. *NeuroRx*: 2006(1);3:3–9.

Panel I (Part I)

Perspectives of 50 Years of Brain Research and Drug Discovery
2:00 p.m. – 3:30 p.m.

The Science of Clinical Psychopharmacology

Karl E. Rickels, M.D.

University of Pennsylvania School of Medicine

Members of the Early Clinical Drug Evaluation Units (ECDEU), as the New Clinical Drug Evaluation Units (NCDEU) was called 50 years ago, contributed significantly in the sixties and seventies to the development of clinical trial methodology. Many of these early research groups were supported by the National Institute of Mental Health (NIMH). These efforts assumed even more urgency in 1962 with the Kefauver-Harris Amendment to the Food, Drug and Cosmetics Act, which instructed the Food and Drug Administration (FDA) to consider not only *safety* but also *efficacy* in the drug approval process.

These early methodological developments are reflected in three collaborative efforts carried out by members of ECDEU, NIMH, and American College of Neuropsychopharmacology (ACNP). Two of these are books on Trial Methodology, published by NIMH and edited by Levine, et al (1971),¹ and Levine (1979).² The third publication represents a several years-long project, guided by Wittenborn.³ These guidelines have been helpful for many years to both pharmaceutical industry and FDA. The next NIMH and ACNP sponsored collaboration to update the state of the art of clinical trial methodology was not published until 1994 by Prien and Robinson.

This presentation will critique present day clinical trial methodology, address the issue of “seemingly” increasing placebo rates over time as well as increased rates of failed clinical efficacy trials. The author will offer recommendations to improve present day trial methodology based on the author’s long term experiment in the field.⁴

Learning Objectives:

- Understand early history of clinical trial methodology
- Understand present state of clinical trial methodology

Literature References:

1. Levine, Schiele and Bouthilet, editors. Principles and problems in establishing the efficacy of psychotropic agents. Public Health Service Publication No 2138; 1971.
2. Levine, editor. Coordinating clinical trials in psychopharmacology. DHEW Publication; 1979. p. 79–803.
3. Wittenborn, editor. Guidelines for clinical trials of psychotropic drugs. Pharmacopsychiatry 1977;10:205–31.
4. Robinson DS, et al. Concerns about clinical drug trials. J Clin Psychopharm 2000;20:593–96.



Panel I (Part II)

Perspectives of 50 Years of Brain Research and Drug Discovery

3:45 p.m. – 5:15 p.m.

History of the Changing Roles of NIMH and Industry Sponsored Studies in Drug Development: Implications for the Future

William Z. Potter, M.D., Ph.D.

Formerly of Merck and Company, Inc.

50 years ago the rationale for, design of, power analyses for and general implementation issues around double blind placebo controlled trials were articulated and debated by investigators who for the next two decades led the field either from the Psychopharmacology Research Branch (PRB, originally the Service Center or PSC) of the NIMH or from university and Veteran Administration Hospital settings. NCDEU brought all of these leaders together as well as colleagues from industry. By the late 1960's most of the standards and themes with which utilize and discuss today were established and applied to efficacy studies of a range of phenothiazine antipsychotics and tricyclic antidepressants. A substantial proportion of efficacy studies were sponsored by the NIMH or VA during this period. In the case of lithium, all seminal efficacy studies in the United States were funded by the NIMH and carried out in either Intramural or Extramural settings, notably maintenance studies in the 70's. By 1976, two decades its inception, the PRB had made available several psychopharmacologic trial assessment, study design and implementation manuals through the Government Printing Office. These were the fruits of citizen advocacy and Congressional support in 1956. Thus, through the mid-70's, government had a leading role in pharmacologic studies of serious mental illnesses. The one area where industry had taken the lead was in the study of anxiolytics, benzodiazepine's being an early triumph of its scientists and chemists. That success laid the foundation for industry research institutes in psychopharmacology beginning in the 70's, such as one from Roche and another from Merck. These, however, were laboratory based efforts focused on discovering and synthesizing novel drugs as well as applying the latest science from academia. Clinical efficacy trials, more and more funded and implemented by industry from the mid-70's, nonetheless followed the principles laid down by the PRB.

For the next two decades, the era of SSRIs and then atypical antipsychotics, industry more and more took the lead in studies of antidepressants and antipsychotics and well as anxiolytics. NIMH did stimulate research on manic-depressive illness, OCD and childhood and geriatric psychopharmacology with industry quickly following the opportunity to register the same drugs used for other disorders in these conditions. By the 90's, industry followed a highly successful strategy for refining the major classes of drugs and marketing them for an increasingly wide range of indications. NCDEU more and more became a forum for presenting and debating issues relevant to addressing clinical need and optimal use of agents introduced by industry: e.g. maintenance treatment, dose response, range of indications, combination and therapies.

Despite the apparent success of numerous "me better" drugs derived from a few core pharmacologic classes, there were questions as to the true efficacy and/or superiority of one drug compared to another. It turned out that drug placebo differences were not so great as to provide much opportunity for showing one drug to be different from another and clinical trial methodologic issues emerged as a major theme by the end of the 90's. In parallel, there was a growing appreciation that the expected novel drugs from the molecular biology revolution of the 80's were not materializing. Moreover, the expanded use of the newer branded drugs, raised questions as to whether they were worth the added costs. During the last decade, the NIMH sponsored major effectiveness studies in schizophrenia, depression and manic-depressive illness, which have had considerable impact as the results became available over the last several years. Moreover, in partnership with the FDA and industry, the Institute led the MATRICS effort to develop a cognitive battery which could be used to register a drug for "cognition in schizophrenia". Over the same period, industry did invest some in methodological studies to try to increase signal detection and find ways of better discriminating between drugs, work that has been highlighted at NCDEU meetings. But most recently, there have been announcements of substantial reductions of industry investment in early psychopharmacology drug development, their research institutes long judged a failure from a business viewpoint. The NIMH had already begun to fund programs related more directly to drug development and appears ready to support the entire bench to bedside enterprise in some areas.

The shifting roles of government, academia and industry have resulted in both periods of productive synergistic collaboration and reactive withdrawal into a more parochial focus. Fortunately, there are many initiatives to better align academia, NIH, industry and the FDA going beyond the model envisaged 50 years ago to better realize the potential of the complex worlds of basic molecular science, systems biology, translational biomarkers and computer based technologies for multiple components of clinical studies.

Learning Objectives:

Literature References:

Clinical Trial Methodologies and Pharmaceutical Development

Angelo N. Sambunaris, M.D.

Atlanta Institute of Medicine and Research

The serendipitous discoveries of chlorpromazine, monoamine oxidase inhibitors and tricyclic antidepressants in the 1950s were a benchmark for all future research in psychopharmacology. It has also been an important clinical lesson that these discoveries resulted from clinical observation of patients, not controlled trials. The inadequacy of the methods at that time heralded the Early Clinical Drug Evaluation Units (ECDEU), a branch of the National Institute of Mental Health. Rapid advances in the laboratory paralleled a paradigm shift in our clinical research methods.

Despite significant advances in psychopharmacologic research, clinical results have yielded few major therapeutic breakthroughs, yet clinical methods have changed extensively over this time period. There have been many failures of drug development, with only relatively modest improvements over the therapeutic agents discovered in the 1950s.

Corporations rather than universities now lead the field of discovery and development. Typically corporations foster a low risk drug development environment while in pursuit of blockbuster compounds. At the same time the ethical and regulatory burden has increased immensely on the process of drug development, detracting from the research advances we have made.

Learning Objectives:

- Provide a conceptual framework for the scientific methods that led to the serendipitous discoveries and compared to the modern scientific methods in vogue today
- Provide a conceptual framework for the ethical, regulatory and clinical hurdles faced by sponsors today
- Discuss limitations of current methods and recommendations for change in order to advance the treatment of mental disorders.

Literature References:

Spiegel, R. Psychopharmacology: an introduction. West Sussex, UK: Wiley and Sons; 2003.
 Healy, D. The creation of psychopharmacology. Cambridge, MA: Harvard University Press; 2004.

Panel 2

Novel and Emerging Endpoints in Child Psychopharmacology Research

2:00 p.m. – 3:30 p.m.

Panel Overview

Joan Busner, Ph.D.

Pennsylvania State University College of Medicine and
United BioSource Corporation

This panel will discuss, from a variety of differing perspectives, endpoints in child and adolescent psychopharmacology trials that are novel and that expand the focus of drug treatment outcome beyond changes in core symptom ratings. The first presenter will discuss the increasing use of sleep measures including polysomnography to detect treatment effects in the Food and Drug Administration (FDA) regulated child and adolescent psychopharmacology trials. The second presenter will discuss cognitive endpoints in child and adolescent psychopharmacology trials, and will discuss some of the indications for which these endpoints are best suited. The third presenter will discuss the public health relevance of treatment endpoints in the National Institute of Mental Health funded research as compared with other perspectives, such as research conducted for regulatory purposes. The last presenter will discuss emerging biological and psychosocial outcome domains and the role they may eventually play in the provision of improved clinical child psychiatric care. A panel discussion with active audience participation will follow the presentations.

Learning Objectives:

- Recognize some of the newer efficacy outcomes currently in development or use in child psychopharmacology trials
- Recognize some of the factors that may render an endpoint less suitable for a registration trial than for a trial under another aegis or funding source
- Understand better some of the means by which expanded endpoints might ultimately assist in clinical provision of care

Sleep in Childhood and Adolescent Psychopharmacology

Suresh Kotagal, M.D.

Mayo Clinic

Sleep-wake patterns can reflect underlying biochemical and neurophysiologic changes. The disturbances of mood, circadian rhythms and attention that are seen in children and adolescents can be associated with alterations in sleep architecture or in the timing of sleep. Further, the effects of psychopharmacologic agents on the central nervous system can be evaluated in both the ambulatory and laboratory setting by the study of sleep, making sleep not only a diagnostic but an efficacy endpoint. The objective of this presentation will be to critically review:

- (1) The type of alterations in sleep wake function that accompany attention deficit hyperactivity disorder, childhood depression and delayed sleep phase syndrome.
- (2) The utility of actigraphy and cyclic alternating patterns (CAP) in pediatric psychopharmacologic research. CAPs are scored from the electroencephalogram, reflect periodic arousals from non-rapid eye movement sleep, and are a more robust marker of sleep fragmentation than quantitative changes in the traditional sleep stages.
- (3) The limitations in the application of the above diagnostic tools of somnology to pediatric psychopharmacology.

Learning Objectives:

- Recognize emerging sleep endpoints such as CAP and their use as efficacy endpoints for child psychopharmacologic trials
- Understand the role of sleep architecture in childhood attention deficit hyperactivity disorder and depression

Literature References:

- Robert JJT, et al. Sex and age differences in sleep macroarchitecture in childhood and adolescent depression. *Sleep* 2006;29:351–58.
- Morgenthaler T, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. *Sleep* 2007;30:519–29.

Panel 2

Novel and Emerging Endpoints in Child Psychopharmacology Research

2:00 p.m. – 3:30 p.m.

Cognition in Child and Adolescent Psychopharmacology Trials

Keith A. Wesnes, Ph.D

Northumbria University and United BioSource Corporation

Cognitive function is increasingly being assessed as a safety and efficacy outcome for new treatments in a wide range of clinical and medical conditions in children and adolescents. The assessment of cognition in children and adolescents poses unique problems including developmental maturation over time. For the Food and Drug Administration-regulated psychopharmacology trials, it is critical that cognition measurements be reliable, valid, treatment-sensitive and age-corrected. Evidence will be presented from a database of over 8,000 children aged six to 17, which indicates that marked maturation changes occur year by year in core aspects of cognitive function in normal children from six years onwards. These changes are not trivial, for example, Power of Attention, an extensively validated reaction time measure of the ability to focus attention, will improve on average from 2000 msec in a six-year-old to under 1500 msec in just two to three years, an effect size approaching one. Other aspects of attention, working memory and episodic memory show developmental changes and will be reviewed. Finally, emerging pediatric indications for cognitive endpoints will be discussed, including autism, attention deficit hyperactivity disorder and childhood schizophrenia.

Learning Objectives:

- Recognize the emerging use of cognitive endpoints in pediatric psychopharmacology trials
- Understand some of the methodologic issues involved in determining appropriate cognitive endpoints for registration trials
- Appreciate how cognitive testing can be conducted in children, and the relevance of the testing for everyday behaviour

Literature References:

Clinical trials in children, for children. *Lancet* 2006;35:1953.
Edgar CJ, et al. Cognition assessment in pediatric clinical trials. *Drug Discov Today* 2008;13:79–85.

Emerging Endpoints in Treatment Research: Different Targets from Different Perspectives

Benedetto Vitiello, M.D.

National Institute of Mental Health

Traditionally, pediatric psychopharmacology research has used symptom reduction as the primary outcome of clinical trials. With increasing attention to the comparative effectiveness of interventions, other outcomes have been identified that are more practically relevant to the usual clinical settings rather than to research units. Thus, remission and functional recovery, in the case of depression, and time to drug discontinuation, in the case of schizophrenia, have been used. Focusing on these outcomes, however, implies conducting trials of longer duration and larger sample size, and the availability of appropriately sensitive rating instruments. Of special interest have been approaches that can integrate both effectiveness and safety outcomes as a way of evaluating the benefit/risk ratio of interventions. This presentation will discuss novel treatment endpoints in light of recent research in children and adolescents.

Learning Objectives:

- Learn about the most recent treatment research in children
- Provide broader and more clinically relevant research results

Literature References:

Vitiello B, et al. Effects of treatment on level of functioning, global health, and quality of life in depressed adolescents. *J Am Acad Child Adolesc Psychiatry* 2006;45:1419–26.
Aman, et al. Medication and parent training in children with pervasive developmental disorders and serious behavior problems. *J Am Acad Child Adolesc Psychiatry* 2009. Forthcoming.

Panel 2

Novel and Emerging Endpoints in Child Psychopharmacology Research

2:00 p.m. – 3:30 p.m.

The Role of Functional Outcomes in Open Follow-Up Designs

Laurence L. Greenhill, M.D.

Columbia College of Physicians and Surgeons, Columbia University

Pediatric psychopharmacology research, both in academia and in the Food and Drug Administration registration trials, has moved from short-term controlled trials, for efficacy purposes, to a broader concept of study that includes long-term, open-label safety trials. Internal validity for double-blind, randomized, placebo-controlled trials benefitted from a single primary efficacy outcome measure, which was selected to be a severity measure of the a symptom characteristic of the categorical disorder being treated. However, safety studies require larger samples of children or adolescents studied over much longer periods of time, thus making it more feasible and ethically better to employ open-label designs. Emerging concepts of the development course of psychiatric disease as children grow from school age through adolescence to adult life suggest that levels of psychosocial functioning may allow a better interpretation of outcome over time than do symptoms levels. Examples will be drawn from National Institute of Mental Health-supported, multisite trials of children and adolescence that suggest that open label trials, using different analytic models, such as propensity analyses and growth mixture models that can include multidimensional outcomes rather than a single symptom measure may provide important information about the long-term compliance with treatment interventions, changing patterns of symptoms and new moderators of outcome.

Learning Objectives:

- Explore multidimensional methods for aligning symptom severity data with problems in functioning during treatment trials
- Explore the relevance of open trial follow-up measures for studying the natural course of childhood psychiatric disorders

Literature References:

- Wigal T, et al. Safety and tolerability of methylphenidate in preschool children with ADHD. *J Am Acad Child Adolesc Psychiatr* 2006;45(11):1294–1304.
- Brent D, et al. The treatment of adolescent suicide attempters study: predictors of suicide events in an open treatment trial. *J Am Acad Child Adolesc Psychiatr* 2009 Aug 26;48:987–96.
- Abikoff HB, et al. Treatment-related changes in objectively measured parenting behaviors in the multimodal treatment study of attention-deficit/hyperactivity disorder. *J Consult Clin Psychol* 2006 Aug;74(4):649–57.
- Molina BS, et al. MTA Cooperative Group. The MTA at 8 years: prospective follow-up of children treated for combined type ADHD in a multisite study. *J Am Acad Child Adolesc Psychiatry* 2009 May;48(5):484–500.



Panel 3

Current Evidence for Effective Pharmacological Suicide Prevention Treatment

2:00 p.m. – 3:30 p.m.

Panel Overview

Stephen H. Koslow, Ph.D.

American Foundation for Suicide Prevention

Paul J. Clayton, M.D.

American Foundation for Suicide Prevention

In 2006 (latest available data), there were 33,300 reported suicide deaths. Suicide is the fourth leading cause of death for adults between the ages of 18 and 65 years in the United States, with 27,321 suicides. Suicide is often characterized as a response to a single event or set of circumstances. But from approximately 120 psychological autopsies, we know that more than 90 percent of the people who kill themselves have a psychiatric disorder. The factors that lead to an outcome of suicide are diverse and complex, so our efforts to understand it must incorporate many approaches. Currently there is discussion on the effectiveness of using different pharmacological approaches to prevent suicide in the mentally ill patient. Questions have been raised about the safety of using antidepressants, lithium, anticonvulsants and antipsychotic medications. The presentations will show data supporting the safety and efficacy of treating patients with clozapine, lithium and anticonvulsants. Lastly, quantitative measures of neurobiological function on the mechanism of lithium will be presented from experiments using an endophenotype approach in mice, which have the potential to unravel the pathways germane to lithium's protective action.

Learning Objectives:

- Learn about safe and effective treatments for suicide prevention
- Learn about mechanisms of action of pharmacological agents used to prevent suicide
- Examine genetic approaches to the study of molecular mechanisms underlying suicide

The Evidence for and Potential Impact of Clozapine on Suicide Risk in Schizophrenia: So How Do We Get Psychiatrists to Prescribe It?

Jean-Pierre Lindenmayer, M.D.

Nathan S. Kline Institute for Psychiatric Research and Manhattan Psychiatric Center, New York University

Suicide is the leading cause of premature death among patients with schizophrenia. Overall, these patients have approximately a 50% lifetime risk for suicide attempts, and a 9–13% lifetime risk for completed suicide. A pivotal study of clozapine, which showed reduced suicidality in patients with schizophrenia, led to the Food and Drug Administration (FDA) indication of clozapine in patients with schizophrenia and suicidality. This multi-center, randomized, international study comparing clozapine and olanzapine was conducted in 980 non-refractory patients with schizophrenia or schizoaffective disorder who were at high risk for suicide were followed for two years. The risk for a suicide attempt or hospitalization to prevent suicide was significantly less in patients treated with clozapine compared to olanzapine (hazard ratio=0.74, p=0.02). In addition, in comparison to treatment with olanzapine, clozapine-treated patients showed fewer suicide attempts (p=0.03), required fewer rescue interventions to prevent suicide (p=0.01) and required fewer hospitalizations to prevent suicide (p=0.05). In spite of this FDA indication, clozapine use among clinicians has remained relatively low. We will explore reasons for this low use both from the clinicians' and the patients' point of view and specific remedies on how to overcome it.

Learning Objectives:

- Understand the role of clozapine in reducing the incidence of suicide attempts and suicidality in patients with schizophrenia
- Better understand resistances against using clozapine and how to remedy them in the treatment of patients with schizophrenia and suicidality

Literature References:

Meltzer HY, et al. Clozapine treatment for suicidality in schizophrenia: international suicide prevention trial (InterSePT). Arch Gen Psychiatry 2003 Jan;60:82–91. Erratum in: Arch Gen Psychiatry 2003 Jul;60(1):735.
Bourgeois M, et al. Awareness of disorder and suicide risk in the treatment of schizophrenia: results of the international suicide prevention trial. Am J Psychiatry 2004;161:1494–96.

Panel 3

Current Evidence for Effective Pharmacological Suicide Prevention Treatment

2:00 p.m. – 3:30 p.m.

Association Between Consistent Purchase of Anticonvulsants or Lithium and Suicide Risk: A Longitudinal Cohort Study from Denmark, 1995–2001

Eric G. Smith, M.D., M.P.H.
University of Massachusetts Medical School

Background: Prior studies suggest anticonvulsants purchasers may be at greater risk of suicide than lithium purchasers.

Methods: Longitudinal, retrospective cohort study of all individuals in Denmark purchasing anticonvulsants (valproic acid, carbamazepine, oxcarbazepine or lamotrigine) (n=9952) or lithium (n=6693) from 1995–2001 who also purchased antipsychotics at least once (to select out nonpsychiatric anticonvulsant use). Poisson regression of suicides by medication purchased (anticonvulsants or lithium) was conducted, controlling for age, sex, and calendar year. Confounding by indication was addressed by restricting the comparison to individuals prescribed the same medication: individuals with minimal medication exposure (e.g., who purchased only a single prescription of anticonvulsants) were compared to those individuals with more consistent medication exposure (i.e., purchasing >5 prescriptions of anticonvulsants).

Results: Demographics and frequency of anticonvulsant, lithium or antipsychotic use were similar between lithium and anticonvulsant purchasers. Among patients who also purchased antipsychotics at least once during the study period, purchasing anticonvulsants more consistently (>5 prescriptions) was associated with a substantial reduction in the risk of suicide (RR=0.22, 95% CI=0.11–0.42, $p<0.0001$), similar to patients consistently purchasing lithium (RR=0.27, 95% CI=0.12–0.62, $p<0.006$). Absolute suicide risks of consistent anticonvulsant and consistent lithium purchasers were similar.

Limitations: Lack of information about diagnoses and potential confounders, as well as other covariates that may differ between minimal and consistent medication purchasers, are limitations to this study.

Conclusions: In this longitudinal study of anticonvulsant purchasers likely to have psychiatric disorders, consistent anticonvulsant treatment was associated with decreased risk of completed suicide.

Learning Objectives:

- Understand strengths and weaknesses of previous longitudinal studies investigating lithium or anticonvulsants and suicide risk
- Understand the strengths and weaknesses of our particular study and Danish national data for addressing this question

Literature References:

- Smith EG, et al. Association between consistent purchase of anticonvulsants or lithium and suicide risk: a longitudinal cohort study from Denmark, 1995–2001. *J Affect Disord* 2009;117:162–7.
- Søndergård L, et al. Mood-stabilizing pharmacological treatment in bipolar disorders and risk of suicide. *Bipolar Disord* 2008;10:87–94.

Translating Suicide Endophenotypes Shared between Humans and Mice: Novel Strategies to Understand the Mechanism Underlying Lithium's Antisuioidal Efficacy

Todd D. Gould, M.D.
University of Maryland School of Medicine

Few treatments have shown convincing reductions in the rates of suicide. An evidence-based exception is that lithium is effective in reducing the risk of both attempted and completed suicide. However, the mechanisms underlying lithium's antisuioidal actions are unknown, limiting the development of improved treatment approaches.

Suicide is a complex behavior that is often difficult to study in humans and impossible to reproduce in animal models. The endophenotype approach, by which quantitative measures of neurobiological function are used to assess and subclassify psychiatric illness, may present a path to new discoveries. Aggression and impulsivity are candidate endophenotypes with known genetic connections and strong associations with suicide; the evidence supporting aggression and impulsivity as suicide endophenotypes, as well as the effects of lithium on these constructs in both humans and rodents, will be reviewed. The mouse may be useful as a model organism to elucidate points of convergence between the actions of lithium on mouse behaviors and known biobehavioral factors associated with human suicide. However, rather than attempting the infeasible task of modeling suicide per se in mice, we will focus on approaches that assess mouse behavior in tests relevant to well validated endophenotypes associated with suicide including aggression and impulsivity. These endophenotypes can be used in combination with human genetic, biochemical and pharmacological findings in suicide research. In particular, data from preclinical and human genetic studies indicate that lithium may exert some of its mood stabilizing effects through inhibition of the enzyme glycogen synthase kinase-3 (GSK-3).

This presentation will discuss current knowledge of lithium pharmacology (including GSK-3) that may be used to dissect the molecular and neurobiological mechanisms mediating lithium's efficacy. Ultimately, the data derived from this line of investigation should promote the development of improved pharmacological interventions to modify aggressive and impulsive behaviors and in turn decrease the risk of suicide.

Learning Objectives:

- Describe endophenotypes associated with suicide
- Understand molecular mechanisms whereby lithium may be exerting antisuioidal efficacy

Literature References:

- Kovacsics CE, et al. Lithium's antisuioidal efficacy: elucidation of neurobiological targets using endophenotype strategies. *Annu Rev Pharmacol Toxicol* 2009;49:175–98.
- O'Donnell KC, et al. The behavioral actions of lithium in rodent models: leads to develop novel therapeutics. *Neurosci Biobehav Rev* 2007;31:932–62.

Panel 4

Somatic Treatments Research: Electroconvulsive Therapy (ECT) and the Future of Brain Stimulation Interventions

3:45 p.m. – 5:15 p.m.

Panel Overview

Matthew V. Rudorfer, M.D.

National Institute of Mental Health

Nonpharmacologic somatic treatments for mental disorders are among both the oldest and the newest approaches in the therapeutic armamentarium. The basic premise established in the 1930s, of the therapeutic potency of a series of grand mal seizures, induced with an electrical stimulus applied to the scalp, has remained constant to the present. Today the use of electroconvulsive therapy (ECT) is commonly relegated to severe mood disorders where medications are ineffective or need to be avoided, although the “gold-standard” potency and speed of response of ECT inform its use earlier in the treatment hierarchy in urgent or life-threatening situations. Advances in ECT technique over the years, including general anesthesia and muscle relaxation, have eradicated some of the serious adverse effects that plagued this intervention in its early days. Considerable research has led to refinements in ECT device properties and clinical approaches to reduce the known cognitive toxicities of standard ECT while retaining its therapeutic benefits; chief advances have included modifications of electrode placement and stimulus waveform and intensity. Although informed consent is routine, continued stigma and uneven availability of ECT result in underutilization. Recent research has focused on methods to reduce the early relapse common after completion of an ECT course, including, currently under study, medication combined with the personalized, flexible application of continuation ECT. Given its ease of transmission through the skull, permitting localized application, magnetic waves have emerged as a promising new means of therapeutic brain stimulation for depression. The success of nonconvulsive repetitive transcranial magnetic stimulation (rTMS), now cleared by the Food and Drug Administration (FDA) for selected cases of medication-unresponsive depression, has led to promising ongoing investigation of the more potent magnetic seizure therapy (MST). Lessons learned during the evolution of ECT, combined with advances in neuroscience, are ushering in a new generation of translational and somatic treatment development research.

Learning Objectives:

- Understand the history of ECT and its role in modern psychiatric therapeutics
- Appreciate the interaction between advances in the understanding of the neurobiology of mental disorders and the development of novel methods of therapeutic brain stimulation techniques

From ECT to Early Clinical Drug Evaluation Units (ECDEU)

Matthew V. Rudorfer, M.D.

National Institute of Mental Health

A mainstay of inpatient treatment in the era preceding the psychopharmacology revolution, electroconvulsive therapy (ECT) was widely assumed to be on the way out by the time the Early Clinical Drug Evaluation Units (ECDEU) program was launched a quarter-century after the first therapeutic convulsion was induced with an injection of camphor in oil. Although the unpredictability of pharmacconvulsive treatment was ameliorated with a switch to electrically-induced seizures in 1938, serious problems remained, from the frightening nature of the intervention and reports of its inappropriate application for behavior control, to compression fractures of the spine, confusion, and memory loss—drawbacks kept alive in the public consciousness for decades through graphic depictions in the novel and movie, *One Flew Over the Cuckoo's Nest*. Encouraging the search for solutions to these problems, rather than discarding this novel treatment, was the unparalleled efficacy of a course of ECT—generally not for its original indication of schizophrenia, but primarily for severe mood disorders: depression (including melancholic and psychotic subtypes), mania, and catatonia, even (and especially) in the face of medication resistance or avoidance. With the introduction of general anesthesia, muscle relaxation, and informed consent to the treatment procedure, many of the early fears and concerns of ECT abated. The search for optimal methods of inducing therapeutic seizures while minimizing adverse cognitive effects and preventing early relapse was to consume the field for a generation, in a research endeavor still ongoing. But will newer methods of brain stimulation—with or without seizure induction—one day replace ECT?

Learning Objectives:

- Gain an appreciation of the history of ECT and the evolution of its role in the treatment of severe mood disorders
- Understand how advances in the technique of inducing seizures during a course of ECT helped reduce the toxicity of the treatment and thereby optimize the benefit:risk ratio and enable the safe and effective use of ECT in appropriately selected individuals in an outpatient setting

Literature References:

National Institutes of Health/National Institute of Mental Health consensus development conference: electroconvulsive therapy (June 1985). *Psychopharmacol Bull* 1986;22:455–502.

Potter WZ, et al. Electroconvulsive therapy—a modern medical procedure. *N Engl J Med* 1993;328:882–83.

Panel 4

Somatic Treatments Research: Electroconvulsive Therapy (ECT) and the Future of Brain Stimulation Interventions

3:45 p.m. – 5:15 p.m.

ECT in the 21st Century: Present State of the Evidence

Charles H. Kellner, M.D.

Mount Sinai School of Medicine

Electroconvulsive therapy (ECT) continues to be widely practiced and is regarded as the most effective treatment for major depression. Procedural and technical refinements make it better tolerated and safer than ever before. The scientific and clinical evidence base for ECT is large; searching “electroconvulsive therapy” on PubMed returns nearly 10,000 citations. Clinical trials and basic laboratory studies have investigated many aspects of the treatment, from clinical predictors of response to optimal electrical waveforms and biomarker changes.¹ The National Institute of Mental Health (NIMH)-supported trials have led to the development of a substantial database on efficacy, optimal electrode placement and stimulus dosing,² and the role of maintenance ECT.³ An ongoing study, Prolonging Remission in Depressed Elderly (PRIDE) is investigating the efficacy of a flexible maintenance ECT schedule, combined with medications.⁴ This presentation will review selected major clinical and research findings from the ECT literature of the last four decades. Despite the impressive breadth and depth of this literature, important areas for further research remain. These include the elucidation of the exact mechanism of action of ECT’s antidepressant and antipsychotic effects and technical refinements to further reduce effects on cognition. ECT continues to be underutilized because of lingering misperceptions about the way the treatment is performed and how the informed consent process occurs in contemporary ECT practice. Given the overwhelming importance of major depression as a public health problem and the unique position of ECT as a treatment for the most severe forms of depression, these issues of stigma require urgent and ongoing attention.

Learning Objectives:

- Understand the clinical use of continuation and maintenance ECT
- Define and identify the problem of stigma in ECT, and how it limits use of this treatment modality

Literature References:

1. Rudorfer MV, et al. ECT alters human monoamines in a different manner from that of antidepressant drugs. *Psychopharmacol Bull* 1988;24(3):396–9.
2. Sackeim HA, et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *N Engl J Med* 1993;328(12):839–46.
3. Kellner CH, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). *Arch Gen Psychiatry* 2006;63(12):1337–44.
4. Lisanby SH, et al. Toward individualized post-electroconvulsive therapy care: piloting the Symptom-Titrated, Algorithm-Based Longitudinal ECT (STABLE) intervention. *J ECT* 2008;24:179–82.

Back to the Future: Brain Stimulation in Psychiatry

Sarah H. Lisanby, M.D.

College of Physicians and Surgeons, Columbia University

Brain stimulation spans our oldest and newest therapies in psychiatry. From the early days of electroconvulsive therapy (ECT) to the recent Food and Drug Administration (FDA) approval of transcranial magnetic stimulation (TMS), brain stimulation represents a family of novel interventions that together play a unique role in psychiatric therapeutics. Brain stimulation represents an interdisciplinary approach spanning engineering, neuroscience, and psychiatry. Engineering advances enable an exciting new array of methods with which to stimulate the brain and induce seizures in a controlled and precise fashion. Neuroscience advances in understanding the neurobiology underlying psychiatric disorders provide therapeutic targets for focal neuromodulation. Psychiatry faces the challenge of defining the appropriate role of brain stimulation in clinical treatment algorithms. Research platforms for the rational design of pharmaceutical interventions can now be applied to the development of novel brain stimulation technologies, and to the re-examination of the gold-standard—ECT. Indeed, recent work suggests that the targeting and individualization of ECT dosage can be optimized through innovations in pulse shape, train characteristics, electrode placement, and amplitude adjustment. In this respect, the future of ECT is being shaped by modern approaches to treatment development. Likewise, the future of novel brain stimulation approaches, such as magnetic seizure therapy (MST), is being shaped by the heritage of ECT research emphasizing the importance of the seizure to antidepressant efficacy. This presentation will review new developments in brain stimulation, including TMS, MST, and experimental forms of ECT, and highlight how each of these have been informed, and in some cases were presaged, by the history of ECT.

Learning Objectives:

- Identify the latest developments in novel brain stimulation therapeutic interventions
- Discuss the more promising new directions for novel treatment development

Literature References:

- George MS, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry* 2010 May;67(5):07–16.
- Peterchev AV, et al. ECT stimulus parameters: rethinking dosage. *J ECT*. Forthcoming.
- Rowny SB, et al. Translational development strategy for magnetic seizure therapy. *Exp Neurol* 2009 Sep;219(1):27–35.
- Spellman T, et al. Focal electrically administered seizure therapy: a novel form of ECT illustrates the roles of current directionality, polarity, and electrode configuration in seizure induction. *Neuropsychopharmacol* 2009 Jul;34(8):2002–10.

Panel 5

Cardiometabolic Effects of Antipsychotics: Mechanisms, Interventions, Gaps and Directions
3:45 p.m. – 5:15 p.m.

Panel Overview

Lawrence A. Maayan, M.D.

Nathan S. Kline Institute for Psychiatric Research and New York University School of Medicine, Child Study Center

Christoph U. Correll, M.D.

The Zucker Hillside Hospital and Albert Einstein College of Medicine

Combining new data from preclinical research, clinical trials and a meta-analysis, this panel aims to: (1) explore mechanisms and risk factors for the wide-ranging cardiometabolic effects of antipsychotics; and (2) examine the effects of behavioral and pharmacologic treatment options.

The first speaker will discuss his current findings on polymorphisms conferring vulnerability to antipsychotic weight gain and directions for future research.

The second speaker will present data on the effectiveness of a one-year behavioral weight management program in 318 adults, comparing adults with psychotic disorders treated with antipsychotics (N=47) with a group of obese adults with other psychiatric conditions (N=49) or without psychiatric comorbidity except for eating disorders (N=222).

The third speaker will present findings from the largest meta-analysis of 32 studies of pharmacologic treatments of antipsychotic weight gain and metabolic abnormalities (n=1487), showing a modest effect for five of the 15 tested interventions compared to treatment as usual.

The final speaker will discuss assessment of cardiac risk and present data on the referral patterns and early metabolic outcomes from an ongoing, randomized trial comparing integrated medical management of obese psychiatric patients with the metabolic syndrome with usual clinical care.

Learning Objectives:

- Learn about the genetics underlying antipsychotic adverse cardiometabolic effects, exploring their relevance for novel drug targets
- Compare the adherence to and efficacy of a behavioral weight intervention in antipsychotic-treated adults with obese patients in the general population followed in the same program
- Apply the findings from a meta-analysis of adjunctive medications for antipsychotic-associated cardiometabolic effects, exploring implications for further research
- Learn about an integrated medical management approach to weight gain and metabolic and cardiac abnormalities in antipsychotic-treated patients

Antipsychotic Pharmacogenetics—Genetic Predictors of Weight Gain and Metabolic Abnormalities

Jeffrey R. Bishop, Pharm.D., B.C.P.P.

University of Illinois, Chicago

Weight gain and the development of metabolic syndrome are increasingly recognized side effects of second generation antipsychotic agents. Antipsychotic-associated weight gain differs across medications and exhibits a high degree of interpatient variability. Second generation agents known to induce the most weight gain are clozapine and olanzapine, followed by risperidone and quetiapine, and then ziprasidone and aripiprazole. However there are many patients who do not gain significant weight from olanzapine and clozapine therapy and similarly there are cases of extreme weight gain seen with seemingly weight neutral agents. Therefore, employing a pharmacogenetic strategy to identify patients who may be at either higher or lower risk for metabolic abnormalities from these agents may help clinicians more empirically choose antipsychotics.

Weight gain is thought to result in part from the antagonism of 5HT2C and H1 receptors which decreases satiety and increases appetite drive. Antipsychotic-treated individuals also exhibit abnormalities in the satiety hormone, leptin, which increases after drug exposure and remains elevated during treatment. Most pharmacogenetics research of antipsychotic weight gain has focused on variants in the promoter of the serotonin-2C receptor gene HTR2C.¹ Additionally, variants in the leptin gene (LEP) and leptin receptor gene (LEPR) have been described as individual or interacting predictors of weight gain from antipsychotics.²

In this session, the pharmacogenetics of antipsychotic-associated weight gain will be explored. In particular, the impact of gene polymorphisms leading to altered 5HT2C, leptin and leptin receptor activity will be discussed. Recent developments in the pharmacogenetics of antipsychotic-associated weight gain and the potential utility of examining metabolic syndrome pharmacogenetics will be presented with a discussion on the clinical implications of the data.

Learning Objectives:

- Examine pharmacologic mechanisms of antipsychotic-associated weight gain and metabolic abnormalities
- Discuss genetic predictors of antipsychotic-associated weight gain and directions for future research

Literature References:

1. De Luca V, et al. Association of the HTR2C gene and antipsychotic induced weight gain: a meta-analysis. *Int J Neuropsychopharmacol* 2007;10(5):697–704.
2. Ellingrod VL, et al. Leptin and leptin receptor gene polymorphisms and increases in body mass index (BMI) from olanzapine treatment in persons with schizophrenia. *Psychopharmacol Bull* 2007;40(1):57–62.

Panel 5

Cardiometabolic Effects of Antipsychotics: Mechanisms, Interventions, Gaps and Directions

3:45 p.m. – 5:15 p.m.

Effectiveness of a Behavioral Weight Management Program in Obese Patients with Psychotic Disorders Versus Obese Patients from the General Population

Christoph U. Correll, M.D.

The Zucker Hillside Hospital and Albert Einstein College of Medicine

Background: Despite high obesity rates, studies of behavioral weight loss interventions in psychiatric patients are sparse and lacking for trials including obese populations without primary psychiatric disorders.

Methods: A 12-month, prospective study of weekly group or individual cognitive-behavioral weight management sessions in 222 obese patients (mean age: 49.2±14.1 years, 34% male, body mass index (BMI): 43.7±9.6) with psychotic spectrum disorders (PSD, n=47), other psychiatric disorders (OPD, n=49), or no psychiatric disorders (NPD, n=126).

Results: During the one-year follow-up, PSD patients had significantly less attrition (51.1%) and longer treatment duration (8.7±4.4 months) than OPD (87.6%, 5.4±4.3 months) and NPD (87.8%, 4.9±4.7 months) patients ($p<0.01$). In observed cases analyses, groups were similar regarding absolute and relative decrease in weight and body mass index (BMI) at all time points. In last-observation-carried-forward (LOCF) analyses, PSD patients experienced significantly greater reductions in percent baseline weight at 12 months (5.1±9.3%) compared to the other groups (2.7± 5.5% and 2.4± 6.3%) ($p<0.05$), BMI at nine months and 12 months compared to NPD patients ($p<0.05$), and percent BMI change and >5% weight loss at nine and 12 months compared to both groups ($p<0.05$). Weight loss >5% occurred in 42.6% of PSD patients versus 18.4% and 23.0% in OPD and NPD patients ($p<0.01$). The strongest weight loss predictor was treatment duration. Baseline depression predicted shorter treatment duration.

Conclusions: Severe psychiatric disorders and treatment with weight inducing medications did not impair weight loss success while engaged in treatment. Due to better adherence, PSD patients had superior weight outcomes at LOCF. Adherence and depression should be targeted to improve obesity outcomes.

Learning Objectives:

- Appreciate the interface between psychiatric disorders and obesity
- Review efficacy of behavioral weight loss programs in psychiatry
- Compare weight loss data in the obese with antipsychotic-induced weight gain with the obese in the general population

Literature References:

- Alvarez-Jiménez M, et al. Non-pharmacologic management of antipsychotic-induced weight gain: systematic review and meta-analysis. *Br J Psychiatry* 2008;101–7.
- Loh C, et al. A comprehensive review of behavioral interventions for weight management in schizophrenia. *Ann Clin Psychiatry* 2006;23–31.

Comparing Pharmacologic Interventions to Reduce Antipsychotic-Related Weight Gain and Metabolic Abnormalities Using Comprehensive Meta-Analytic Data

Lawrence A. Maayan, M.D.

Nathan S. Kline Institute for Psychiatric Research and New York University School of Medicine, Child Study Center

Background: Antipsychotic treatment is limited by weight gain and metabolic abnormalities. Efficacy data for pharmacologic augmentation strategies to minimize antipsychotic-related weight are confined to mostly small scale studies.

Methods: Systematic review and meta-analysis comparing pharmacological weight loss treatments added to anti-psychotics against placebo. Primary outcomes included weight and body mass index. Secondary outcomes included >7% weight gain, change in waist circumference and glucose lipid metabolism parameters.

Results: Thirty-two randomized studies with 1,482 subjects testing 15 different agents were identified. Metformin was associated with the greatest weight loss compared to placebo (N=7, n=334, -2.94 kg [CI: -4.89,-0.99]), followed by d-fenfluramine (N=1, n=16, -2.60 kg [CI: -5.14,-0.06]), sibutramine (N=2, n=55, -2.56 kg [CI: -3.91,-1.22]), topiramate (N=2, n=133, -2.52 kg [CI: -4.87,-0.16]) and reboxetine (N=2, n=79, -1.90 kg [CI: -3.07,-0.72]). Data for metabolic outcomes were sparse. Interventions initiated after weight gain had occurred yielded greater weight loss than preventive treatments started concomitantly with antipsychotics.

Conclusions: Five of 15 medications outperformed placebo, although the effect was modest. Safer antipsychotics and novel interventions for adverse antipsychotic cardiometabolic effects are needed.

Learning Objectives:

- Become familiar with current data describing pharmacologic strategies to treat antipsychotic weight gain
- Understand directions for further research based on strengths and weaknesses of previous trials

Literature References:

- Maayan L, et al. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. *Neuropsychopharmacology* 2010 March 24. [Epub ahead of print].
- Baptista T, et al. Pharmacological management of atypical antipsychotic-induced weight gain. *CNS Drugs* 2008;22:477–95.

Panel 5

Cardiometabolic Effects of Antipsychotics: Mechanisms, Interventions, Gaps and Directions
3:45 p.m. – 5:15 p.m.

Pharmacologic Interventions to Reduce the Cardiometabolic Risk and Sudden Cardiac Death in Antipsychotic-Treated Patients

Peter Manu, M.D.

The Zucker Hillside Hospital and Albert Einstein College of Medicine

Background: Antipsychotic weight gain is associated with metabolic syndrome, cardiac risk and obesity.

Methods: Review of medical management of glucose and lipid abnormalities and cardiac risk in the context of psychotropic treatment.

Results: Patients with elevated low-density lipoprotein (LPL) cholesterol should start on pravastatin which ameliorates glucose intolerance and is not metabolized by CYP450 3A4. Elevated non-high-density lipoprotein (HDL) cholesterol after statin therapy should be treated with fenofibrate. Low HDL after the correction of LDL and non-HDL cholesterol should be treated with nicotinic acid. Irbesartan, an angiotensin receptor blocker is used for BP > 129 mm Hg systolic or 84 mm Hg diastolic with a calcium channel blocker if needed. Thiazide diuretics and beta-blockers should be avoided. Electrocardiogram (EKG) should be obtained at baseline to assess for pre-existing ischemic disease and conduction abnormalities including prolonged QTc. For postprandial hyperglycemia (140-199 mg/dl after two hrs), metformin, a biguanide with insulin-sensitizing properties can be used. Thiazolidindiones can be used second line. Therapy can be augmented with alpha-glucosidase inhibitors. Treatment of weight gain can start with orlistat, a partial lipase inhibitor producing lipid malabsorption. Sibutramine, a serotonin and norepinephrine reuptake inhibitor, may be used adjunctively, with monitoring for serotonin syndrome and treatment-emergent hypertension.

Conclusions: Metabolic management should allow for medication interactions.

Learning Objectives:

- Describe the therapeutic targets in patients with metabolic syndrome
- Evaluate randomized controlled trials of drug therapy for lipid and glucose abnormalities associated with metabolic syndrome

Literature References:

- Correll CU, et al. Equally increased risk for metabolic syndrome in patients with bipolar disorder and schizophrenia treated with second-generation antipsychotics. *Bipolar Disord* 2008;10:788–97.
- Correll CU, et al. Identification of high-risk coronary heart disease patients receiving atypical antipsychotics: single low-density lipoprotein cholesterol threshold or complex national standard? *J Clin Psychiatry* 2008;69:578–83.



Panel 6

Combining Medication with Psychosocial Intervention to Improve Outcome of Axis I Disorders

3:45 p.m. – 5:15 p.m.

Panel Overview

Ira D. Glick, M.D.

Stanford University School of Medicine

Ellen Frank, Ph.D.

Western Psychiatric Institute and Clinic, University of Pittsburgh

For almost as long as there have been drug treatments for psychiatric disorders, researchers have been exploring the possible benefits of combining them with psychotherapy. In the context of the 50th anniversary of the New Clinical Drug Evaluation Units (NCDEU), this panel will present an historical overview of controlled outcome studies of combining medication with psychosocial interventions for Axis I disorders in four areas: (1) depressive disorders, (2) bipolar disorder, (3) anxiety disorders, and (4) schizophrenia. Most, but not all controlled trials, have shown an increased efficacy of psychotherapy added to medication, compared to either treatment alone. We will review the methodologies used in each of these areas, compare results within and across them and suggest questions that remain to be answered and strategies for answering them in future trials areas.

The session will be dedicated to the memory of Mike Goldstein, Phil May, Gerry Klerman and Jerry Hogarty—pioneers in this research.

Learning Objectives:

- Be informed of the latest controlled data on combining medication with psychosocial interventions for Axis I disorder
- Understand the limitations of the data and new directions for research

Combining Medication and Psychotherapy for Unipolar Depression: Is There a Clear Benefit?

Ellen Frank, Ph.D

Western Psychiatric Institute and Clinic, University of Pittsburgh

The idea of combining psychotherapy with pharmacotherapy for the treatment of depression dates back almost as far as the New Clinical Drug Evaluation Units (NCDEU) meeting, but as treatment resources and clinician time become increasingly scarce, it is worth considering when and how best to combine psychotherapy with pharmacotherapy in the treatment of mood disorders. This presentation will review trials comparing monotherapies with combination for the treatment of unipolar disorders and will focus on the various ways in which these two treatment approaches have been combined in the outpatient and inpatient treatment of unipolar affective disorders. Data will also be presented to support the value of a sequenced approach to the outpatient treatment of unipolar disorder in which the clinician begins with either pharmacologic or psychotherapeutic monotherapy and moves to combination treatment when monotherapy fails to produce sustained remission. With respect to maintenance treatment, most studies suggest that the combination is required only for more vulnerable or complicated populations such as the elderly or those with so-called double depression.

Learning Objectives:

- Be familiar with the various trials in which pharmacotherapy has been combined with a disorder-specific psychotherapy in the treatment of unipolar depression and dysthymia
- Be familiar with the relative value of beginning treatment with combination therapy versus sequencing monotherapy with combination when monotherapy alone is not successful in bringing about remission

Literature References:

- Hollon, SD, et al. Psychotherapy and medication in the treatment of adult and geriatric depression: Which monotherapy or combined treatment? *J Clin Psychiatry* 2005;66:455–68.
- Frank, E, et al. Interpersonal psychotherapy and antidepressant medication: evaluation of a sequential treatment strategy in women with recurrent major depression. *J Clin Psychiatry* 2000;61:51–7.

Panel 6

Combining Medication with Psychosocial Intervention to Improve Outcome of Axis I Disorders
 3:45 p.m. – 5:15 p.m.

Adjunctive Psychotherapy for Bipolar Disorder: Findings from Across the Lifespan

David J. Miklowitz, Ph.D.
 David Geffen School of Medicine, University of California, Los Angeles

Psychotherapy has long been recommended as adjunctive to pharmacotherapy for bipolar disorder. The current questions concern which interventions are effective for which patients, over what intervals and for what domains of functioning. This talk will emphasize randomized trials of adjunctive psychotherapy for bipolar disorder. There are currently 19 published trials of individual and group psychoeducation, systematic care, family therapy, interpersonal therapy and cognitive behavior therapy (CBT). Relevant outcome variables have included time to recovery, recurrence, duration of episodes, symptom severity and psychosocial functioning. Generally, the trials have found that adjunctive psychotherapy enhances the symptomatic and functional outcomes of bipolar disorder over two-year periods. The effects of the treatment modalities have varied according to the clinical condition of patients at the time of random assignment and the polarity of symptoms at follow-up. Family-focused therapy (FFT), interpersonal and social rhythm therapy (IPSRT) and systematic care appeared to be most effective in preventing recurrences when initiated after an acute episode, whereas CBT and group psychoeducation appeared to be most effective when initiated during a period of recovery. The various modalities differ in content, structure and associated mediating mechanisms. Recent research has demonstrated the role of psychotherapy in the treatment of early-onset bipolar disorder in children and adolescents. The role of psychotherapy within chronic care algorithms and as a preventative agent in the early stages of the disorder deserve investigation.

Learning Objectives:

- Discuss the research concerning the efficacy of psychotherapy in patients with bipolar disorder
- Identify major clinical strategies associated with psychoeducation, communication training, and problem-solving as relevant to bipolar disorder
- Recognize the role of psychotherapy in the treatment of early onset bipolar illness

Literature References:

Miklowitz DJ. Adjunctive psychotherapy for bipolar disorder: state of the evidence. *Am J Psychiatry* 2008;165(11):1408–19.
 Miklowitz DJ, et al. Psychosocial treatments for bipolar disorder: cost-effectiveness, mediating mechanisms, and future directions. *Bipolar Disord* 2009;11:110–22.

Combination Treatment with Medication and Psychotherapy for Anxiety Disorders

M. Katherine Shear, Ph.D.
 Columbia University School of Social Work

Great strides have been made over the past half century in the treatment of anxiety disorders. Both medication and cognitive behavior therapy (CBT) are proven efficacious for panic disorder, social anxiety disorder, obsessive compulsive disorder and post traumatic stress disorder. These approaches work by different mechanisms, and it makes sense that using them together would be optimal. This presentation will provide an overview of some of the studies of combination treatment for anxiety disorders, including similarities and differences across the disorders and will discuss the relative benefits of antidepressant medication, cognitive behavioral therapy and their combination. Novel approaches to combining medication and CBT will also be discussed.

Learning Objectives:

- Discuss the benefits of combination treatment compared to medication alone
- Discuss the benefits of combination treatment compared to CBT alone
- Consider the benefits of sequential compared to concomitant use of medication and CBT
- Discuss novel strategies for medication and psychotherapy combination

Literature References:

Foa, et al. Randomized, placebo-controlled trial of exposure and ritual prevention, clomipramine, and their combination in the treatment of obsessive-compulsive disorder. *Am J Psychiatry* 2005;162:151–61.
 Barlow, et al. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. *JAMA* 2000;283:2529–34.

Panel 6

Combining Medication with Psychosocial Intervention to Improve Outcome of Axis I Disorders
3:45 p.m. – 5:15 p.m.**Combining Medication with Psychosocial Intervention to Improve Outcome of Schizophrenia****Ira D. Glick, M.D.**

Stanford University School of Medicine

Although psychotropic medications introduced in the 1950s revolutionized the treatment of schizophrenia, they produced only partial response from baseline function. The issue has been, what does psychotherapeutic intervention add (over medication alone) to improve outcome for patients and families? This paper will review the methodologies and types of psychotherapies used, compare results within and across them and suggest questions and strategies to answer them.

There is strong evidence that long-term family intervention and moderate evidence for cognitive behavior therapy (CBT), both used in combination with medication, are a more effective treatment for schizophrenia than medication alone. They are associated with significant reductions in relapse and rehospitalization rates. However, combining family intervention with different medication dosage strategies, in one study, did not change outcome.

Learning Objectives:

- Be informed of the latest controlled data on combining medication with psychosocial interventions for schizophrenia
- Understand the limitations of the data and new directions for research

Literature References:

Mueser KT, et al. Family treatment and medication dosage reduction in schizophrenia: effects on patient social functioning, family attitudes and burden. *J Consult Clin Psychol* 2001;69:3–12.

Glick ID. Adding psychotherapy to pharmacotherapy: data, benefits, and guidelines or integration. *Am J Psychother* 2004;58:186–208.



Plenary Session II

The Genetics of Schizophrenia and Bipolar Disorder—Implications for Treatment Development
10:45 a.m. – 12:15 p.m.

Keynote Address

Edward M. Scolnick, M.D.

The single largest risk factor for schizophrenia and bipolar illness is genetic risk. First degree relatives of probands with either illness have a seven- to 10-fold elevated risk of having the index illness and in addition the other illness. Many attempts to decipher the underlying genetics over many decades have yielded confusing and irreproducible results. With the exception of the Disrupted in Schizophrenia (DISC) gene in a particular Scottish family, no clear evidence has existed for the role of any human gene in the pathophysiology of any psychotic illness, and no population-based evidence has been rigorously proven. With the technologies and platforms developed in human genetics in the first decade of the 21st century, the opportunity to unravel fully the underlying genetic architecture of psychotic illness is upon us. Unless this is accomplished, the field will be mired in outdated approaches to discover new medicines, frozen with purely descriptive symptomatic diagnostic categories, with inadequate proof of the biological basis of these illnesses to wipe away the stigma facing patients, and with inadequate political strength to convince budget decision makers to infuse sums into the field adequate to drive innovative quantal improvements for patients and families. I will discuss progress in the last three years in the human genetics of schizophrenia and bipolar illness, point out why we are at a unique inflection point for rapid progress and explain how a focused effort on defining the full genetic architecture can lead to both better treatments and better services for patients and families.

Learning Objectives:

- Understand the importance of genetics to drug discovery
- Recognize the properties of an ideal drug
- Learn about the revolution in human genetics and how it is transforming psychiatric research on psychotic illness



New Investigator Graduate Symposium: Translational Perspectives on Treatment Development

10:45 a.m. – 12:15 p.m.

Symposium Overview

Barry D. Lebowitz, Ph.D.

University of California, San Diego School of Medicine

Mark H. Rapaport, M.D.

Cedars-Sinai Medical Center and University of California, Los Angeles

The National Institute of Mental Health Director Thomas Insel, M.D., has described the movement of the field toward a "Decade of Translation." This symposium builds upon that theme and highlights the contributions of the New Investigator Program to NCDEU and to the field as a whole. Three themes in translational research are highlighted: the reciprocal interaction of bench and clinic to inform treatment discovery, conditions promoting the selection of individualized treatment strategies to advance the personalization of care and barriers to the use of research-based evidence to guide clinical decision making and patterns of practice. Three recent alumni of the program illustrate these themes in their own work, and discuss directions for the field in the coming decade.

Learning Objectives:

- Symposium attendees will develop greater appreciation of the complex and reciprocal roles of basic science, clinical research, and health services research in the translational research perspective
- Symposium attendees will develop greater appreciation of the barriers to translation and to optimal use of research evidence to inform practice and policy

Proof of Concept: Neurobiological Clues for Treatment Development – Treatment Clues for Neurobiological Pursuit

Dan V. Iosifescu, M.D.

Massachusetts General Hospital, Harvard Medical School

Purpose: The search for novel treatments in mood disorders with new mechanisms of action will need to be informed by our understanding of the underlying neurobiology. We will present an example from our research on abnormal brain bioenergetics in major depressive disorder (MDD). Previous studies using phosphorus magnetic resonance spectroscopy (31P-MRS) have shown abnormal brain energy metabolism in subjects with MDD, characterized by decreases in brain beta nucleoside triphosphate (NTP) levels (primarily representing adenosine triphosphate [ATP] in the brain) with normal or slightly elevated levels of phosphocreatine (PCr). Thyroid hormones have been used effectively as augmentation treatment in MDD, but the mechanism of their antidepressant effect is not understood. In hypothyroid individuals thyroid hormones increase muscle and brain bioenergetic metabolism and mitochondrial function.

Methods: We will present two studies where brain 31P MRS was collected from MDD subjects before and after antidepressant treatment. In the first study (N=19) the antidepressant treatment was thyroid hormone, T3, while in the second study it was the SSRI escitalopram (N=62).

Results: Beta-nucleoside triphosphate (beta-NTP) levels are lower in MDD subjects compared to controls, suggesting a pattern of mitochondrial dysfunction in MDD. Such bioenergetic abnormalities appear to be corrected after successful antidepressant treatment with either thyroid hormones or escitalopram. Changes in the levels of the main neurotransmitters (GABA, glutamine) are also associated with antidepressant response in MDD. Improvement in brain energy stores (beta-NTP) is associated with, and may be necessary for, increases in brain neurotransmitter levels.

Importance: These studies support the role of mitochondrial dysfunction in mood disorder. This justifies testing pharmacological agents and devices with demonstrated in-vitro or in-vivo enhancement of mitochondrial activity as potential treatments for mood disorders. Measures of bioenergetic metabolism could be used in the screening of new compounds with putative antidepressant activity.

Learning Objectives:

- Describe changes in mitochondrial function and brain bioenergetic metabolism associated with treatment response in major depressive disorder
- Name two pharmacological agents or devices which have mitochondrial enhancing activity and may be potential antidepressant treatments

Literature References:

Iosifescu DV, et al. Brain bioenergetics and response to triiodothyronine augmentation in major depressive disorder. *Biol Psychiatry* 2008;63(12):1127–34.

Jensen JE, et al. Triacetyluridine (TAU) decreases depressive symptoms and increases brain pH in bipolar patients. *Exp Clin Psychopharmacol* 2008;16(3):199–206.

New Investigator Graduate Symposium: Translational Perspectives on Treatment Development
10:45 a.m. – 12:15 p.m.

**Personalizing Treatments for Bipolar II Disorder:
The Right Treatments for the Right People**

Holly A. Swartz, M.D.
University of Pittsburgh School of Medicine

Background: Little empirical evidence exists to guide informed treatment decisions for individuals with bipolar (BP) II disorder. Psychotherapy may play an important role as monotherapy for a subgroup of individuals with BP II (in contrast to BP I) who, obviating the need for drug exposure, can be successfully managed with psychotherapy alone. We hypothesize that interpersonal and social rhythm therapy (IPSRT) could have such a role in the treatment of BP II depression.

Empirical Findings: We recruited unmedicated individuals meeting DSM-IV criteria for BP II disorder, currently depressed. In Trial 1, subjects (n=17) were treated openly with IPSRT for 12 weeks. In Trial 2, subjects (n=22) were randomly assigned to 12 weeks of either IPSRT or quetiapine. In Trial 1, 41% (n=7) of the sample responded to IPSRT monotherapy ($\geq 50\%$ reduction in depression scores without an increase in mania scores), 41% (n=7) dropped out of the study and 18% (n=3) did not respond to treatment. Data collection is nearing completion in Trial 2.

Discussion: IPSRT is a feasible treatment for a subset of individuals with BP II depression. The real challenge, however, will be to determine, a priori, who can be treated safely with psychotherapy alone and who will require medication. We hypothesize that characterizing individuals with BP II as "more unipolar-like" to "more BP I-like" on the affective disorders continuum may predict for whom psychotherapy mono-therapy will suffice. Relevant moderating variables may include circadian phase preference, intercurrent hypomanic symptoms during depressive episodes, number of previous episodes, family history of mood disorders, and prior response to antidepressant medications. We also hypothesize that use of functional magnetic resonance imaging (fMRI) to compare neural mechanisms of the BPII, BP I, and unipolar disorders may help elucidate the affective disorders spectrum, ultimately paving the way toward developing combined clinical and neurophysiologic profiles to personalize treatments.

Learning Objectives:

- Recognize the importance of developing individualized approaches to treat bipolar II disorder
- Recognize the role of psychotherapy in the management of bipolar II disorder

Literature References:

Swartz HA, et al. Psychotherapy as monotherapy for the treatment of bipolar II depression: a proof of concept study. *Bipolar Disord* 2009;11:89–94.
Leon AC. Two clinical trial designs to examine personalized treatments for psychiatric disorders. *J Clin Psychiatry*. Forthcoming.

**Changing Practice: We Know What to Do;
How Do We Get it Done?**

Christoph U. Correll, M.D.
The Zucker Hillside Hospital and Albert Einstein College of Medicine

Background: Translating research findings into clinical practice has remained a difficult task. Examples include the appropriate use of clozapine in refractory patients with schizophrenia, the avoidance of antipsychotic polypharmacy, as well as the appropriate monitoring and management of therapeutic and adverse effects of medication. Cardiometabolic adverse effects of the widely used second-generation antipsychotics, which have been linked to a shortening of life expectancy, have become an increasing focus of concern. This has resulted in a label change of antipsychotics by the Food and Drug Administration and in detailed and widely promulgated monitoring guidelines by several professional organizations around the world.

Methods: Review of guidelines and guideline adherence for cardiometabolic monitoring and management of patients treated with antipsychotics in general clinical practice settings. Discussion of difficulties in translating research knowledge into clinical practice. Review of the efficacy and challenges of educational/behavioral campaigns.

Results: Five recent pharmacoepidemiologic and claims database studies have reconfirmed that the warning and guideline production by the American Diabetes Association in conjunction with the American Psychiatric Association and other organizations has had only a negligible impact regarding increasing cardiometabolic monitoring behaviors in antipsychotic treated patients. In fact, monitoring rates in adults with severe mental disorders initiating antipsychotics were indistinguishable from a control population of adults without psychiatric conditions initiating albuterol treatment. Educational and regulatory measures were ineffective, except for reduced prescribing of olanzapine. Data suggest that it is difficult to succeed in encouraging additional behaviors that may be perceived as time and resource intensive.

Conclusions: Alternative approaches to translating research knowledge into clinical practice are needed. Clinician decision making, behavior and motivational incentives need to be studied in more detail and novel programs need to be implemented and tested. Linking reimbursement to quality indicators and targeted peer group pressure to improve quality care should be formally tested.

Learning Objectives:

- Appreciate the need for guideline-driven, measurement-based psychiatry
- Review the results on guideline adherence by practitioners, exemplified by the routine cardiometabolic monitoring of patients receiving antipsychotics
- Discuss novel educational and behavioral program approaches that can help translate research findings into clinical practice

Literature References:

Morrato EH, et al. Metabolic testing rates in 3 state Medicaid programs after FDA warnings and ADA/APA recommendations for second-generation antipsychotic drugs. *Arch Gen Psychiatry* 2010 Jan;67(1):17–24.
Haupt DW, et al. Prevalence and predictors of lipid and glucose monitoring in commercially insured patients treated with second-generation antipsychotic agents. *Am J Psychiatry* 2009 Mar;166(3):345–53.
Morrato EH, et al. Metabolic risk status and second-generation antipsychotic drug selection: a retrospective study of commercially insured patients. *J Clin Psychopharmacol* 2009 Feb;29(1):26–32.

Panel 7

Pharmacotherapy of Severe Aggression in Children and Adolescents

10:45 a.m. – 12:15 p.m.

Panel Overview

Vivian Kafantaris, M.D.

The Zucker Hillside Hospital and Feinstein Institute for Medical Research

Severe aggression remains the most common reason for psychiatric emergency department visits, hospitalizations and out-of-home placement for children and adolescents. Despite the prevalence of this disabling symptom nearly all medications used to treat explosive aggression are prescribed off-label. The three panelists will present findings from their recently completed National Institute of Mental Health funded clinical trials in children with different primary diagnoses, for whom severe explosive aggression was the primary target of treatment. All three studies had either open or single blind lead-in phases. The first presenter will present data demonstrating that half the children with attention deficit hyperactivity disorder (ADHD) plus oppositional defiant disorder or conduct disorder (CD) had an excellent response to optimized stimulant monotherapy during the lead-in phase, so they did not enter the placebo-controlled study of adjunctive treatment with divalproex. The next presenter will present data from a placebo-controlled study of lithium in adolescents with explosive aggression associated with CD in which lithium was not superior to placebo. The results from this outpatient trial contrast with those from an earlier trial conducted with hospitalized children. Another presenter will present pilot data that suggest that adjunctive treatment with a second generation antipsychotic medication may not offer effective prophylaxis against severe aggressive episodes associated with bipolar I disorder. Finally, there will be a discussion of the methodological issues that impede the generalizability of research in this area before opening up the discussion to audience participation.

Learning Objectives:

- Learn about the evidence base supporting the use of medications to reduce aggression in youth across diagnoses
- Learn about the methodological issues that impede the generalizability of research in this area

Stimulant-Responsive and Stimulant-Refractory Aggression among Children with Attention Deficit Hyperactivity Disorder (ADHD)**Joseph C. Blader, Ph.D.**

Stony Brook State University, New York School of Medicine

Aggressive, dyscontrolled rageful episodes in response to minimal provocation are a highly prevalent and disabling presentation among child psychiatric patients. Although occurring in the context of diverse psychiatric and developmental disturbances, the deficits in impulse control characteristic of attention deficit hyperactivity disorder (ADHD) make youngsters with this disorder especially vulnerable to aggressive behavior. Treatment of aggressive behavior among youth with antipsychotic and other medications has proliferated. Although stimulant treatment has beneficial effects on other disruptive behavior symptoms, the magnitude of stimulant effectiveness in meaningfully attenuating aggressive behavior per se among children with identifiably severe aggression that is the chief concern of clinical attention is uncertain. This evidentiary gap may contribute to the widespread perception that severe volatility and aggression are "more than ADHD" and therefore increase the alacrity with which clinicians initiate alternative nonstimulant pharmacotherapy that carries larger adverse effect liabilities.

This presentation highlights findings from a clinical trial for highly aggressive youth with ADHD and included an open-label stimulant optimization lead-in that endeavored to establish refractoriness of aggression to stimulant monotherapy before randomization to adjunctive divalproex sodium or placebo. A brief review of trial methodology and outcomes of the randomized controlled trial (RCT) precedes a detailed examination of the stimulant treatment strategy employed and the outcomes observed during stimulant monotherapy. Forty-eight percent of those beginning the trial experienced diminution of aggression sufficient to preclude the use of additional agents, and most of these youngsters showed full remission of aggression. These improvements were maintained for an additional eight weeks. Auxiliary analyses indicate that reduced aggression during this phase was mediated largely by improvements in impulse control, rather than via reduced affective lability. Remission was more common among children whose baseline ratings on symptoms associated with mood disturbances, adjusted for baseline aggression, were below the median value for the sample. Findings indicate that systematic, well-monitored stimulant titration with prompt adjustments to optimize individual response frequently yield reductions in aggressive dyscontrol that obviate the need for other pharmacotherapy.

Learning Objectives:

- Learn about a systematic, protocol-driven approach to stimulant monotherapy for aggressive youth with ADHD whose goal was to optimize response for this first-line ADHD treatment
- Become informed about the rate of remission with stimulant monotherapy for this patient group, and factors that moderated and mediated reductions in aggressive behavior that accompanied stimulant monotherapy

Literature References:

- Connor D, et al. Psychopharmacology and aggression. I: A meta-analysis of stimulant effects on overt/covert aggression-related behaviors in ADHD. *J Am Acad Child Adolesc Psychiatry* 2002;41:253-61.
- Blader JC, et al. Aggression in children: an integrative approach. In: Martin A, Volkmar FR, eds. *Lewis' Textbook of Child and Adolescent Psych*. 4th ed. Baltimore, MD: Lippincott, Williams, & Wilkins; 2007. p. 467-83.
- Blader JC, et al. Adjunctive divalproex sodium versus placebo for children with ADHD and aggression refractory to stimulant monotherapy. *Am J Psych* 2009;166:1392-401.

Panel 7

Pharmacotherapy of Severe Aggression in Children and Adolescents

10:45 a.m. – 12:15 p.m.

Lithium for Reducing Aggression in Conduct Disorder: Inpatient Versus Outpatient Trial Results

Richard P. Malone, M.D.
Drexel University College of Medicine

We conducted two randomized double-blind and placebo controlled trials of lithium for reducing aggression in youth aged nine to 17 years diagnosed with conduct disorder. One of the key differences between the two trials, which may be related to outcome, was that Study 1 was conducted in an inpatient setting and Study 2 in an outpatient setting. In both studies, subjects had to meet an aggression criterion during a single blind baseline period in order to be randomized to treatments. Study 1 (n=40) was a six-week acute trial that included 40 subjects. Study 2 (n=29) included both a six-week acute trial (Phase 1) following which responders were re-randomized to Phase 2, in which they received long-term treatment with lithium or placebo. In Study 1, lithium was significantly superior to placebo for reducing aggression on the Overt Aggression Scale and the Clinical Global Impression Improvement item. However, in Study 2, there was no advantage for lithium compared to placebo on the same measures. Differences in outcome between the two trials will be discussed.

Learning Objectives:

- Lithium may be effective and safe for reducing aggression in conduct disorder
- The setting of a clinical intervention study may be related to the efficacy outcome

Literature References:

Malone RP, et al. A double-blind placebo-controlled study of lithium in hospitalized aggressive children and adolescents with conduct disorder. *Arch Gen Psychiatry* 2000;57:649–54.
Yudofsky SC, et al. The overt aggression scale for the objective rating of verbal and physical aggression. *Am J Psychiatry* 1986;143:35–9.

Maintenance Treatment with Adjunctive Second Generation Antipsychotics Not Beneficial for Severe Aggression Associated with Bipolar I Disorder in Adolescents

Vivian Kafantaris, M.D.
The Zucker Hillside Hospital and Feinstein Institute for Medical Research

Background: Assaultive or destructive behaviors are frequent precipitants for hospitalization in children and adolescents with bipolar I disorder and these behaviors may have enduring social consequences. Maintenance treatment with the second generation antipsychotic medication (SGA) risperidone has been shown to significantly delay recurrence of disruptive symptoms in children and adolescents with disruptive behavior disorders.¹ However, as we previously reported,² there was little difference in time to recurrence of clinically significant aggression relative to placebo, in contrast to psychotic symptoms during a 48-week placebo controlled maintenance study.

Methods: A Kaplan-Meier survival analysis was used to examine time to recurrence of clinically significant aggressive behavior or psychosis in adolescents who had assaultive/destructive behavior (n=10) or psychotic features (n=11) during their index episode of mania.

Results: Remaining on active SGA, in addition to a mood stabilizer, minimally delayed recurrence of aggression relative to placebo (median nine versus two weeks) but had a greater impact on time to recurrence of psychotic symptoms (median 36 versus eight weeks).

Discussion: The risk benefit ratio of maintenance treatment with an SGA for severe aggression may be less favorable than longer-term treatment with an SGA for psychotic features. Effective treatment for children and adolescents with severe aggression remains an unmet public health need.

Learning Objectives:

- Discuss the risk benefit ratio of long-term treatment with SGA in addition to a mood stabilizer in aggressive youth with bipolar I disorder
- Discuss the need for more efficacious psychopharmacological treatment for aggression in bipolar youth

Literature References:

1. Reyes, et al. A randomized, double-blind, placebo-controlled study of risperidone maintenance treatment in children and adolescents with disruptive behavior disorders. *Am J Psychiatry* 2006;163:402–10.
2. Kafantaris V, et al. Adolescents with psychotic mania may benefit from maintenance treatment with adjunctive SGAs. Poster session presented at: 49th annual NCDEU meeting; 2009; Hollywood, FL.

Individual Research Reports

10:45 a.m. – 12:15 p.m.

Positive Effects of the Nicotinic Channel Blocker TC-5214 as Augmentation Treatment for Patients with Major Depression Who are Inadequate Responders to a First-Line Selective Serotonin Reuptake Inhibitors (SSRI)

Geoffrey C. Dunbar, M.D.
Targacept, inc.

Step 1 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial demonstrated a poor (36.8%) remission rate following citalopram monotherapy. It has been postulated that modulation of the neuronal nicotinic receptor could have antidepressant properties. TC-5214 is a non-competitive nicotinic channel blocker that modulates different forms of the $\alpha 5\beta 2$ neuronal nicotinic receptor subtype in distinct ways. TC-5214 is active in preclinical models of depression. In the present study, an initial 579 patients received eight weeks open-label treatment with the SSRI citalopram hydrobromide. Patients with an inadequate response ($n=270$) were randomized to eight weeks double blind treatment with add-on TC-5214 or add-on placebo. Dosage of TC-5214 could be increased from one mg bid to four mg bid at the investigator's discretion. The trial was undertaken at 20 sites in India and three sites in the United States. The primary outcome measure was mean change from week eight to week 16 on the Hamilton Depression Rating Scale-17 (HAM-D-17). There was a highly statistically significant advantage ($p<0.0001$) in favor of TC-5214 + citalopram over placebo + citalopram on an intent to treat basis. Secondary measures assessed depression, irritability, disability, cognition, severity of illness and global improvement. A highly statistically significant advantage for TC-5214 + citalopram was also seen over placebo + citalopram on all of these secondary measures. The TC-5214 + citalopram treatment combination was generally well tolerated. The most common adverse events for TC-5214 + citalopram in excess of placebo + citalopram were headache, constipation and dizziness, all of which were seen in less than 10% of patients and were of mild to moderate intensity. The results of the study, together with earlier results from a very similarly designed citalopram augmentation trial with racemic mecamylamine, demonstrate the potential for modulation of neuronal nicotinic receptors in the brain as augmentation to first-line therapy as a new treatment paradigm for depression.

Learning Objectives:

- Review nicotinic receptors in depression
- Consider augmentation as treatment for depression

Literature References:

- Rush AJ, et al. Acute and long-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006;163:1905–17.
- Shytle RD, et al. Nicotinic acetylcholine receptors as targets for antidepressants. *Mol Psychiatry* 2002;7:525–35.
- Fedorov AB, et al. Differential pharmacological mecamylamine enantiomers: positive allosteric modulation and noncompetitive inhibition. *J Pharmacol Exp Ther* 2009;328:1–8.
- Lippiello PM, et al. TC-5214 (S-C+)-mecamylamine: a neuronal nicotinic receptor modulator with antidepressant activity. *CNS Neurosci Thera* 2008;14:266–77.

How to Sit on the Shoulders of Giants: The Evolution of Literature Searching

Leslie L. Citrome, M.D., M.P.H.
Nathan S. Kline Institute for Psychiatric Research

In the not-too-distant past, the only accessible way of systematically searching for relevant journal articles was by going to the medical library and pulling down from the reference shelves heavy tomes of *Index Medicus*, a multi-volume printed index of what has been published in the major medical journals. Today, the availability of automated delivery of electronic tables of contents (eTOCs), electronic feeds of targeted search results and workflow tools allow relevant articles to find the reader. Electronic storage and retrieval tools make it possible to manage this information and make day-to-day clinical and research activities more efficient. A novel approach of "intelligent harvesting" of journal articles is described, together with methods of information storage, indexing, backup, retrieving, viewing and sharing.

Learning Objectives:

- Be able to locate electronic resources that "push" information to your computer desktop
- Be able to organize, retrieve and view stored information efficiently and securely
- Understand the potential of new workflow tools that help disseminate information
Help eliminate file cabinets full of paper

Literature References:

- Citrome L, et al. How to search and harvest the medical literature: let the citations come to you, and how to proceed when they do. *Int J Clin Pract* 2009 Sep 11;63:1565–70.
- Citrome L. Creating a more productive, clutter-free, paperless office: a primer on scanning, storage and searching of PDF documents on personal computers. *Int J Clin Pract* 2008;62(3):363–6.
- Citrome L. Impact factor? shmimpact factor! the journal impact factor, modern day literature searching, and the publication process. *Psychiatry* 2007;4(5):54–7.

Individual Research Reports
10:45 a.m. – 12:15 p.m.

Learning from the Past to Bridge Current Health Disparities in Central Nervous System (CNS) Research: Considerations and Implications in Working with Minority and International Communities

Lewis A. Opler, M.D., Ph.D.
Columbia University Medical Center

Multi-national clinical trials have become standard practice over the past decade. However, the impact of cross-cultural differences in psychiatric assessments, diagnoses, and measurements of treatment response has largely been under-researched in the context of randomized clinical trials. Other disciplines (e.g., anthropology, sociology) have consistently highlighted the importance of cultural values/practices in influencing the expressions of distress and help-seeking behaviors. The impact of other group-level factors such as stigma, economics, and cultural competency also merit more serious examination, particularly for CNS studies where issues of cultural biases and misdiagnosis continue to raise questions regarding study results. Race and ethnicity often come into play at site selection, subject enrollment, trial conduct, and study design.

Learning Objectives:

- Review how racial/ethnic minority and international populations are represented and assessed in CNS trials and address ongoing controversies and challenges in diagnosis that may affect clinical trial results
- Facilitate a highly interactive dialogue among workshop presenters and audience members, who will exchange ideas in order to improve representation of ethnic/racial and international samples for future trials

Literature References:

Aglin DM, et al. Racial and ethnic effects on psychotic psychiatric diagnostic changes from admission to discharge: a retrospective chart review. *J Clin Psychiatry* 2008;69:464–69.
Yang LH, et al. Comparing diagnostic methods for mental disorders in China. *Lancet* 2009 Jun 13;373:2002–4.

Antidepressant Agents and Suicide Death: Three Analytic Approaches

Marcia A. Valenstein, M.D.
University of Michigan Health System

Background: Observational data provide sample sizes needed for the examination of suicide risk with different antidepressant agents. However, selection biases must be addressed. We examined suicide death and starts of the seven most commonly used antidepressants for Department of Veterans Affairs (VA) patients in depression care, using three approaches to address selection biases.

Methods: We identified VA patients with depression diagnoses receiving new antidepressant starts between April 1, 1999, and September 30, 2004 (N=502,179). Traditional Cox regression models, models with propensity scoring and instrumental variable (IV) analyses were used to examine the relationship between suicide and starts of bupropion, citalopram, fluoxetine, mirtazapine, paroxetine, sertraline and venlafaxine.

Results: Crude suicide rates varied from 77/100,000 person-years on bupropion to 284/100,000 person-years on mirtazapine. In traditional Cox regression models, adjusting for patient and facility factors, bupropion was associated with a significantly lower risks of suicide than citalopram, mirtazapine, paroxetine, and venlafaxine. Both fluoxetine and sertraline had significantly lower risks than citalopram and paroxetine. Propensity stratified analyses produced similar, although not always significant, results. IV analyses did not confirm pair-wise contrasts.

Discussion: Traditional Cox regression analyses indicated differences in risks of suicide death among antidepressants; citalopram and paroxetine generally had higher risks while fluoxetine, sertraline and bupropion had lower risks. Although consistent with some prior reports, residual confounding may be an issue. Propensity weighted analyses produced similar, but fewer, significant results. IV estimates were not consistent with Cox model or propensity scoring estimates. Divergence in findings by analytic approach suggests caution when using observational data to assess suicide risks associated with antidepressant agents.

Learning Objectives:

- Understand the implications of using different analytic approaches when examining relationships between antidepressant agents and suicide death
- Understand implications of current and past studies regarding differences in risks with antidepressant agents

Literature References:

Barbui C, et al. Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies. *CMAJ* 2009 Feb 3;180(3):291–97.
Jick H, et al. Antidepressants and the risk of suicidal behaviors. *JAMA* 2004 Jul 21;292:338–43.

Individual Research Reports

10:45 a.m. – 12:15 p.m.

Bayesian Adaptive Randomization Design for a Phase 2 Alzheimer's Disease Clinical Trial

Yili L. Pritchett, Ph.D.
Abbott Laboratories

Given the high failure probability in early phase clinical trials, efficient exploration of safety and efficacy of a full dose range of New Molecular Entities (NMEs) is essential. Bayesian adaptive randomization design uses accumulating data to update the randomization ratio in a Bayesian framework periodically during a study such that subjects will be assigned to more informative treatment groups as the trial goes on. This design allows a more precise estimation of a drug effect for a given sample size.

Bayesian adaptive randomization design was used in a recently completed Phase 2 placebo-controlled study of ABT-089, an $\alpha\beta_2$ neuronal nicotinic receptor agonist, assessed as adjunctive therapy in Alzheimer's patients. A Bayesian adaptive randomization algorithm was created to search among six dose groups for ED90 and the Minimum Efficacious Dose. Stopping rules using Bayesian posterior probabilities were used to allow early study termination due to success or futility.

After enrollment of 337 patients, the study was terminated due to futility. No dose group demonstrated a statistically significant improvement compared with placebo on the primary outcome measure.

The Bayesian randomization successfully allocated subjects in a continuously updating manner to support the investigation of potentially more efficacious dose groups, thereby enabling more rapid discerning for futility. With the broad dose range studied, the objective of learning about the compound was sufficiently achieved at the time of termination. Novel designs such as this increase the efficiency of clinical programs.

Learning Objectives:

- Understand value of using Bayesian adaptive randomization design in early phase clinical programs
- Understand design elements of this novel approach for an Alzheimer's disease clinical trial

Literature References:

Berry, DA. Bayesian clinical trials. *Nat Rev* 2006;27–36.
Krams M, et al. Acute stroke therapy by inhibition of neutrophils (ASTIN): an adaptive dose-response study of UK-279,276 in acute ischemic stroke. *Stroke* 2003;34:2443–48.

Methodological Challenges and Advances in Assessing Pediatric Adverse Drug Events

Moira A. Rynn, M.D.
New York State Psychiatric Institute, Columbia University

Psychopharmacological treatments are a leading therapeutic modality for many childhood psychiatric disorders. The controversies concerning the relationship between antidepressants and medications more generally, and suicidal ideation and behavior have underscored the need for better methods for standardized and systematic monitoring of adverse events.

Pediatric clinical trials will be evaluated for the strategies used in ascertainment of adverse events (AEs). Previous work has shown that the typical practice of relying upon general questions to ascertain AEs will miss over half of the events.¹ The Child/Adolescent Anxiety Multimodal Treatment Study (CAMS), compared the efficacy of cognitive behavior therapy (CBT) alone, sertraline alone, pill placebo, and a combination of CBT and sertraline for 488 youth with the diagnosis of a primary anxiety disorder.² The main comparison of reported rates of AEs did not differ significantly between the sertraline and placebo groups. A more detailed examination focusing on the AEs reported between all the treatment arms will be presented. Secondary analyses of the safety data from CAMS will evaluate how the potential ascertainment methods used and treatment expectancies may have contributed to the reporting of AEs.

Finally, a new computerized measure will be presented that can be used to systematically screen for adverse events associated with the use of antidepressant medications with children and adolescents, including suicidal events and symptoms and behavior thought to portend suicide risk.

Learning Objectives:

- Be updated on the methods used in assessing AEs
- Be familiar with how ascertainment methods may impact the collection of AEs

Literature References:

1. Greenhill LL, et al. Comparison of increasingly detailed elicitation methods for the assessment of adverse events in pediatric psychopharmacology. *J Am Acad Child Adolesc Psychiatry* 2004;43:1488–96.
2. Walkup JT, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med* 2008;359:2753–66.

Workshop 7

Suicidality Issues in Clinical Trials

2:15 p.m. – 5:30 p.m.

Workshop Overview

Kelly L. Posner, Ph.D.

New York State Psychiatric Institute, Columbia University

Research and clinical practice have been plagued by methodological limitations regarding suicidal ideation and behavior. Such issues have undermined confidence in epidemiological findings and have had a profound impact on drug safety questions. Concerns in recent years over the relationship between suicidality and medications across multiple indications have led to increasing efforts to assess suicidal outcomes in clinical trials and to gather and appropriately interpret data for pivotal drug analyses. These improved methods of data collection are of critical importance as debunking false notions of risk and accurately identifying true risk are equally crucial from a public health perspective. Despite these improvements, several issues are outstanding.

This workshop will highlight some of the existing challenges and offer potential solutions that have been devised to allow for the practical, effective and nuanced evaluation of suicidality across diverse settings. Issues include determining which outcome measures are key indicators of acute and chronic suicide risk as well as managing suicide risk in clinical trials, particularly in at risk populations. Optimal research designs for risk estimation while balancing ethical considerations and scientific goals will be explored, from both safety and efficacy perspectives.

The relative meaning of suicidal ideation and suicidal behavior as they relate to future risk (e.g., does ideation predict attempts in clinical trials?) will be discussed as well as their regulatory implications. Balancing scientific and practical goals also applies to the question of exclusion of suicidal patients from clinical trials. Since most patients with suicidal ideation or recent suicidal behavior are excluded from pre-marketing clinical trials, the need to find ethical and valid study designs that can include these patients would appear to be important, given that many of these patients will be exposed to the drugs after Food and Drug Administration (FDA) approval. Existing evidence does not seem to warrant exclusion of suicidal patients from clinical trials. Clinical trial suicidologists will review the feasible and effective methods to optimize clinical trial conduct and in turn facilitate desired outcomes.

A more thorough evaluation of the benefits and risks of medications and suicide related outcomes should include a consideration of known or putative risk factors as well as mediating and moderating variables. Suicidal ideation and/or suicidal behavior may be influenced by such factors as: comorbid psychiatric and medical diagnoses, history, genetics and social support systems. Assessment of mediators and moderators should elucidate critical questions regarding suicide; mainly who is in fact at risk, when they are at risk, and finally what factors may play a role in mitigating or increasing that risk.

Novel approaches have been developed to best meet the needs of suicide assessment to the ultimate goal of streamlining data collection while simultaneously monitoring for patient safety. We will discuss the relative strengths and weaknesses of different modalities including: self report, clinician-administered, centralized raters and interactive technology, as well as their integration, to facilitate consistent data outcomes. Innovative assessment approaches towards answering population-specific questions will also be presented.

Discussion of optimal data analytic approaches involving both efficacy and safety in regards to suicidal outcomes will be presented. Preliminary data from studies involving new analytic strategies will also be presented. Innovative solutions to address the limitations of meta-analyses and randomized controlled trials (RCTs) will be reviewed. Among others, the workshop will cover research synthesis (the use of standardized approaches across many data sources, populations and study designs) to improve estimates of magnitude and variability of risk in order to inform researchers, clinicians and regulators.

Current regulatory perspectives, both for efficacy and safety endpoints, will be addressed. Details as well as the implications of the Psychiatry Products Division guidance document for all psychiatric clinical trials will be discussed (e.g., the types of studies and specific diagnostic indications).

Learning Objectives:

- Appreciate the importance of the relative meaning of key outcome variables (ideation and behavior) as predictors of acute and chronic suicide risk
- Better understand the challenge of assessing suicidality in populations that may be at elevated risk and be better equipped to manage ethical concerns in clinical trials where these populations are the target of intervention
- Learn new data analytic strategies for studying risk of suicide in clinical trials
- Learn about innovative assessment approaches

Literature References:

Greenhouse JB, et al. Thinking outside the (black) box: antidepressants, suicidality, and research synthesis. *Pediatrics* 2005;116:231–33.

Meyer, R. et al. Harvard best practices- suicidality and risk of suicide: definition, drug safety concerns and a necessary target for drug development. Forthcoming.

Posner K, et al. Columbia classification algorithm of suicide assessment (C-CASA): classification of suicidal events in the FDA’s pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry* 2007;164:1035–43.

Stone MB, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to U.S. Food and Drug Administration. *BMJ* 2009;339:b2880.

Workshop 7

Suicidality Issues in Clinical Trials

2:15 p.m. – 5:30 p.m.

Methodological Considerations of Suicide Assessment within Clinical Trials**Kelly L. Posner, Ph.D.**

New York State Psychiatric Institute, Columbia University

Concerns over the link between medications and suicidality have led to improvements in the assessment of suicidal ideation and behavior. This presentation will review the value and new advances in the systematic assessment of suicidal ideation and behavior. It will demonstrate how systematic assessment of suicidality is feasible and can add to the efficiency and precision of a trial by providing more reliable outcomes, establishing operationalized criteria for inclusion/exclusion, specifying parameters for triggering referrals thus decreasing unnecessary referral and burden and allowing for the ascertainment of baseline suicidality data, which can improve determination of adverse event/treatment relationships. Establishment of which outcomes indicate elevated suicide risk is a necessary and complex task. Key variables of interest as they relate to clinical trial data and safety and efficacy issues will be discussed. There is a need to find ethical, valid and feasible study designs that can include patients with recent suicidal ideation or behavior who are typically excluded from pre-marketing clinical trials. Once inclusion/exclusion criteria are established, procedures for monitoring and managing actual and potential suicidality must be implemented in clinical trials. Considerations for developing these procedures for specific phases of drug development, as well as for distinct populations, will be reviewed. Prospectively collected suicidality data for psychiatric and non-psychiatric indications will be presented, including lifetime and on-study rates of suicidality. Optimal research designs for risk estimation while balancing ethical considerations and scientific goals will be explored, from both safety and efficacy perspectives. Finally, novel approaches for streamlining data collection while simultaneously monitoring for patient safety will be explored. Some of these approaches include self report, centralized rater systems and interactive technologies.

Learning Objectives:

- Gain an appreciation for the feasibility of the systematic assessment of suicidality in clinical trials
- Learn about novel approaches to optimize data collection while addressing patient safety

Literature References:

Posner K, et al. Columbia classification algorithm of suicide assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry* 2007;164(7):1035–43.

Emslie GJ, et al. Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. *J Am Acad Child Adolescent Psychiatry* 2009;48(7):721–9.

Risk Factors, Mediators and Moderators of Suicidal Behavior**J. John Mann, M.D.**

New York State Psychiatric Institute, Columbia University

A thorough evaluation of the benefits and risks of medications and suicide-related outcomes should include a consideration of known risk factors, as well as mediating and moderating variables. Mediators are intervening variables that help clarify the nature of and represent potential mechanisms that underlie the relationship between independent and dependent variables. Moderators are characteristics that affect the direction and/or strength of the relationship between the independent and dependent variables. Suicidal behavior and ideation-specific mediators and moderators to be considered include: biological factors (genetic, stress responsivity, developmental anomalies, altered neural circuitry), psychological factors (aggressive and impulsive traits, negative inferential styles, cognitive rigidity, hopelessness), psychiatric illness (e.g., major depressive episode) and social support systems. Knowing mediating and moderating relationships affecting risk of suicide helps in understanding factors that play a role in mitigating or increasing that risk and creates a context for evaluating the effects of treatment.

Learning Objectives:

- Learn about risk factors for suicidality and the role of various mediators and moderators in these relationships
- Understand how to incorporate knowledge of such mediators and moderators into evaluation of treatment effects

Literature References:

Mann JJ. Neurobiology of suicidal behaviour. *Nat Rev Neurosci* 2003;4:819–28.

Mann JJ, et al. Suicide prevention strategies: a systematic review. *JAMA* 2005;294(16):2064–74.

Workshop 7

Suicidality Issues in Clinical Trials

2:15 p.m. – 5:30 p.m.

Risk Management of Suicidal Patients in Clinical Trial Research

Gregory K. Brown, Ph.D.

University of Pennsylvania School of Medicine

The presentation will briefly review ethical issues in managing high risk patients in clinical trial research. A brief overview of the informed consent process will be described when enrolling high risk patients in studies that evaluate suicide-related outcomes. Risk management strategies will also be presented that involve conducting a comprehensive risk assessment as well as a brief clinical intervention, safety planning, that can serve as a valuable adjunct to risk assessment for suicidal patients. The safety plan consists of a hierarchically-arranged list of coping strategies identified for use during a suicidal crisis or when suicidal urges emerge. The specific intervention components include: (1) identifying the warning signs associated with crises, (2) identifying internal coping strategies that require patients to distract themselves from their suicidal thoughts, (3) identifying external distractors such as contacting another person or going to a safe social setting, without disclosing suicidal thoughts, (4) identifying individuals to ask for help, (5) identifying professionals or agencies to ask for help, and (6) identifying dangerous aspects of the environment and to delineate specific steps necessary to keep the patient safe.

Learning Objectives:

- Describe issues related to informed consent in working with suicidal patients
- Describe risk management strategies that include risk assessments and a brief intervention (safety planning) that may be used in clinical trial research

Literature References:

Stanley B, et al. Safety planning: A brief intervention to mitigate suicide risk. *Cognitive and Behavioral Practice*. Forthcoming.
Brown GK, et al. Cognitive therapy for the prevention of suicide attempts: A randomized controlled trial. *Journal of the American Medical Association*, 2005;294: 563-70.

An Update on Food and Drug Administration Guidance for Prospective Suicidality Assessment

Thomas P. Laughren, M.D.

Food and Drug Administration

This talk will provide an update on a Food and Drug Administration (FDA) guidance on prospective suicidality assessment in clinical trials. Treatment emergent suicidality (suicidal ideation and behavior) is recognized as a possible adverse effect of treatment with psychiatric and other drugs. Consequently, the Division of Psychiatry Products has developed a guidance document to provide sponsors of investigational new drugs (INDs) advice on how best to monitor for these possible effects in trials conducted under INDs. Such assessments are needed not only to protect patients in clinical studies but also to provide optimal data for future meta-analyses of suicidality data. Studies and populations for which suicidality assessments are needed will be identified, as well as circumstances where exemptions might be considered. Advice on the needed frequency of such assessments will be provided, and also identification of assessment instruments that would be considered acceptable. FDA's criteria for assessing any proposed suicidality assessment instrument will be provided. Finally, general advice will be provided on data management approaches for suicidality data collected in clinical trials.

Learning Objectives:

- Understand FDA requirements for prospective suicidality assessments in clinical trials
- Understand FDA criteria for assessing proposed suicidality assessment instruments

Literature References:

Hammad TA, et al. Suicidality in pediatric patients treated with antidepressants. *Arch Gen Psychiatry* 2006;63:332-39.
Stone M, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to U.S. Food and Drug Administration. *BMJ* 2009;339:b2880.

Workshop 7

Suicidality Issues in Clinical Trials

2:15 p.m. – 5:30 p.m.

Post-Approval Drug Safety Surveillance**Robert D. Gibbons, Ph.D.**

University of Illinois, Chicago

Following the drug-approval process, concerns remain regarding the safety of new drugs that are introduced into the marketplace. In the case of rare adverse events, the number of subjects that are treated in randomized controlled trials is invariably inadequate to determine the safety of the new pharmaceutical. Identifying safety signals for new and/or existing drugs is a major priority in the protection of public health. Unfortunately, design, analysis and available data are often quite limited for detecting in a timely fashion any potentially harmful effects of drugs. In this presentation, we examine a variety of approaches for determining the possibility of adverse drug reactions. Our review includes spontaneous reports, meta-analysis of randomized controlled clinical trials, ecological studies and analysis of medical claims data. We consider both experimental design and analytic problems as well as potential solutions. Many of these methodologies are then illustrated through application to data on the possible relationship between taking antidepressants and increased risk of suicidality.

Learning Objectives:

- Understand statistical methods for drug safety
- Learn experimental design approaches for evaluating drug safety

Literature References:

Gibbons RD, et al. The relationship between antiepileptics and suicide attempts in patients with bipolar disorder. Arch Gen Psychiatry. Forthcoming.

Gibbons RD, et al. Post-approval drug safety surveillance. Annu Rev Public Health 2010;31:419–37.



Panel 8

Innovative Approaches to the Development of Therapeutics for Mental Disorders in Children
 2:15 p.m. – 3:45 p.m.

Panel Overview

Margaret C. Grabb, Ph.D.

National Institute of Mental Health

Traditionally, pharmacological treatments for mental disorders in children involve drugs developed for adults. Advances in scientific methods (e.g., the use of genetically-engineered animal models; non-invasive imaging) have the potential to elucidate the mechanisms underlying mental disorders in children and facilitate the discovery of new or improved therapeutics aimed at developmentally-relevant targets.

The first presenter will highlight lessons learned during development of compounds for treating Fragile X. Study designs and data from studies in juvenile and adult animals will be presented. The approach used to define critical treatment windows will be discussed and preliminary results reported. The second presenter will describe the rationale—based on a mouse model—for an exploratory intervention using an inhibitor of Ras activity to reverse cognitive deficits in Neurofibrominosis type 1 (NF1) and will present findings related to molecular and neural bases of working memory deficits in a mouse model and humans, and preliminary data from a pilot study of treatment effects in humans. Another presenter will highlight the use of functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS) to investigate mechanisms of action of existing pharmacological agents and to identify novel treatment strategies for adolescent mania. She will present preliminary data on the unique neurochemical effects of, and predictors of response to, lithium versus olanzapine. The final presenter will provide an update on current strategies for drug therapy in attention deficit hyperactivity disorder (ADHD) and will discuss the expanding range of neurochemical systems under investigation, and the impact of common genetic variation on treatment response. Background and available data will be presented from recent and ongoing studies using novel treatment approaches.

Learning Objectives:

- Understand how advances in scientific methods are being used to investigate the mechanisms underlying mental disorders in children
- Learn about innovative techniques to evaluate novel treatment approaches targeting childhood mental disorder

Translating Basic Science Research Discoveries into Novel Therapeutics for Children with Fragile X Syndrome

Randall L. Carpenter, M.D.

Seaside Therapeutics

Fragile X syndrome (FXS) is caused by a mutation in the FMR1 gene that prevents expression of the Fragile X mental retardation protein (FMRP). Brain development in the absence of FMRP gives rise to the major symptoms of FXS including impaired cognitive function and development, seizures, anxiety, obsessive-compulsive and autistic behaviors. Understanding the effects of the Fragile X mutation on brain development and function has been facilitated by generation of knockout animal models. The range of phenotypes observed in these animal models suggests that FXS can be conceptualized as a disorder of excess—excessive sensitivity to environmental change, synaptic connectivity, memory extinction, protein synthesis, body growth and excitability. Remarkably, these metabolic, morphologic, synaptic, circuit and behavioral excesses can all be corrected by reducing mGluR5 signaling. The accumulated scientific evidence over the last decade suggests that mGluR5 is a valid target for development of drugs to treat FXS. Safety and efficacy of novel therapeutics is typically first assessed in adults before advancing to younger patient populations. However, treatment of FXS may be more effective when administered to children. The potential for greater efficacy in younger patients must be balanced against the possibility of unique age-related toxicity. This presentation will discuss an approach for gaining insights into age-related tolerability and toxicity by performing studies in juvenile as well as adult animals. An approach to define critical treatment windows during brain development will also be discussed.

Learning Objectives:

- Understand the scientific basis for a potential treatment of FXS
- Understand how preclinical studies can inform development of novel therapeutics for use in children

Literature References:

- Dölen G, et al. Correction of fragile X syndrome in mice. *Neuron* 2007 Dec 20;56(6):955–62.
- Bear MF, et al. The mGluR theory of fragile X mental retardation. *Trends Neurosci* 2004 Jul;27(7):370–7.

Panel 8

Innovative Approaches to the Development of Therapeutics for Mental Disorders in Children

2:15 p.m. – 3:45 p.m.

Neurofibromatosis I as a Model for Therapeutic Neuroadaptation

Carrie E. Bearden, Ph.D.

Semel Institute for Neuroscience and Human Behavior,
University of California, Los Angeles

Developmental learning disabilities present a major public health burden and are associated with substantial psychiatric morbidity. However, to date no effective pharmacologic treatments have been developed for these severely disabling conditions. Neurofibromatosis type 1 (NF1) is a valuable single-gene model for understanding mechanisms of cognitive disability. The development of a mouse model of the disorder led to the key discovery that increased Ras activity is responsible for the learning deficits in NF1. Next, our preclinical studies showed that treatment with lovastatin, which acts as a potent inhibitor of Ras activity and is commonly used for the treatment of hypercholesterolemia, can reverse the cognitive deficits observed in NF1 mice. For the first time, this allows us to assess a pharmacologic treatment for cognitive deficits, using a medication that has been validated in preclinical studies and for which substantial clinical safety data is available. There will be a discussion of recently conducted parallel experiments to further examine the molecular and neural basis of working memory deficits in both the mouse model and human subjects with NF1; these studies provide evidence for a common mechanism related to dysfunction of the inhibitory system. Further discussion of an exploratory treatment study, in which these preclinical findings are being extended to studies in human subjects with NF1, may determine whether analogous changes in brain structure and function are observed following lovastatin treatment in humans.

Learning Objectives:

- Understand the rationale for using lovastatin as a potential treatment for learning and attentional deficits in NF1
- Learn about the way in which single gene disorders can provide a valuable model for understanding mechanisms of cognitive disability, and lead to the development of novel treatments
- Increase understanding of common molecular and neural mechanisms underlying working memory deficits in mice and human patients with NF1

Literature References:

- Li W, et al. The HMG-CoA reductase inhibitor lovastatin reverses the learning and attention deficits in a mouse model of neurofibromatosis type I. *Curr Biol* 2005 Nov 8;15:1961-7.
- Ehninger D, et al. Reversing neurodevelopmental disorders in adults. *Neuron* 2008 Dec 26;60(6):950-60.

Functional Magnetic Resonance Imaging (fMRI) and Magnetic Resonance Spectroscopy (MRS) Markers of Treatment Response and Effects in Adolescent Mania

Melissa P. DelBello, M.D., M.S.

University of Cincinnati College of Medicine

Neuroimaging studies have identified structural, functional and neurochemical abnormalities in ventral prefrontal-amygdala brain regions in adolescents with bipolar disorder. There will be a discussion of how functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS) may be utilized to enhance our understanding of the mechanisms of action of existing pharmacological agents used for the treatment of adolescent mania, as well as to identify novel treatment strategies for manic adolescents. There will be a further discussion of preliminary data suggesting the unique neurochemical effects of and predictors of response to lithium versus olanzapine for the treatment of adolescents with bipolar disorder. For example, proton MRS investigations reveal that an elevation in myo-inositol concentrations predicts lithium response, whereas elevations in choline levels predict olanzapine response. Moreover, following treatment with olanzapine, N-acetyl aspartate is significantly increased in responders as compared to non-responders. In contrast, the opposite pattern is identified with treatment response to lithium.

Learning Objectives:

- Identify the neurochemical effects of treatment with olanzapine in adolescent mania
- Identify neurochemical predictors of treatment response to olanzapine in adolescent mania
- Identify the neurochemical effects of lithium for depression associated with bipolar disorder in adolescence

Literature References:

- DelBello, MP et al. Neurochemical effects of olanzapine in first hospitalization manic adolescents: a proton magnetic resonance spectroscopy study. *Neuropsychopharmacology* 2006 Jun;31(6):1264-73.
- Patel NC, et al. Lithium treatment effects on Myo-inositol in adolescents with bipolar depression. *Biol Psychiatry* 2006 Nov 1;60(9):998-1004.

Panel 8

Innovative Approaches to the Development of Therapeutics for Mental Disorders in Children
2:15 p.m. – 3:45 p.m.

Novel Treatments in Attention Deficit Hyperactivity Disorder (ADHD) Suggested by Biology and Genetics

James T. McCracken, M.D.

Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles and Resnick Neuropsychiatric Hospital

Objectives: This presentation will provide an update on current strategies for drug therapy of attention deficit hyperactivity disorder (ADHD).

Methods: The talk will be based on a review and synthesis of current ADHD treatment research topics. Topics will include: the expanding view of what neurochemical systems underlie disordered functioning in ADHD; the impact of common genetic variation on treatment response; and the status of testing new agents and combinations of treatments to enhance outcomes in ADHD.

Results: Preclinical information suggests that additional pathways beyond dopamine may also be relevant to aspects of ADHD, such as the noradrenergic, orexinergic and GABAergic systems. Knowledge of the mechanism of action of common ADHD treatments has afforded examination of the effects of gene variants on treatment response. Both candidate gene and newly available genome-wide studies suggest that individual variation in response is moderated by genetic effects, with relevant gene variants found in many transmitter systems besides dopamine. Finally, data from several completed and ongoing studies are pointing towards new treatment approaches, including combination treatments which target multiple neurotransmitter systems. Background and available data from these studies will be presented.

Conclusions: A variety of research and theory is supporting the continued evolution of drug therapies for ADHD.

Learning Objectives:

- Highlight the challenge of treatment variability in ADHD and the impact of executive function deficits on outcome
- Discuss strategies for improved ADHD treatment which are developed from basic neuroscience of the regulation of attention and inhibitory networks

Literature References:

- Palumbo DR, et al. Clonidine for attention-deficit/hyperactivity disorder: I. Efficacy and tolerability outcomes. *J Am Acad Child Adolesc Psychiatry* 2008;47:180–8.
- Spencer TJ, et al. Safety and effectiveness of coadministration of guanfacine extended release and psychostimulants in children and adolescents with attention deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2009;19:501–10.



Panel 9

Instrumental Moments: A Historic Overview of Outcome Measure Development in Psychiatric Research 2:15 p.m. – 3:45 p.m.

Panel Overview

Mark G. Opler, Ph.D., M.P.H.
New York University School of Medicine

Nina R. Schooler, Ph.D.
State University of New York, Downstate Medical Center

Various instruments have been adopted as key outcome measures for psychopharmacologic research over the past 50 years. The historical and scientific context in which these measures were developed may be instructive for the challenges we face today as research practice adapts to the needs of the 21st century. As our understanding of psychopathology changes, trialists develop new approaches to measurement of treatment effects. Psychometricians are tasked with the goal of developing measures to be reliable, valid, sensitive or capable of differentiating essential categories with greater accuracy. These measures may be accepted over time, eventually supplementing or supplanting older ones that do not reflect new ideas or fail to meet the practical challenges of research. Broad adoption of a new measure usually requires a paradigm shift (e.g., the recognition of somatic symptoms of depression as a legitimate target for treatment) combined with sharp clinical observation to spur the development and adoption of measures.

The goal of these presentations and panel discussions is to illustrate the challenges of the past and explore key moments wherein new measures were conceived, developed, validated and eventually adopted as standard tools for modern research. The session will begin with a review of the developments that began in the 1960s to create assessment instruments that could be used reliably in a range of settings and trials. The next speaker will discuss the controversies in depression ratings and the emergence of the Montgomery-Åsberg Depression Rating Scale (MADRS) as the new standard for research in affective disorders. There will then be a discussion of the development of the Positive and Negative Symptoms Scale (PANSS) and its role in the psychopharmacology of schizophrenia. The session will conclude with a moderated panel discussion focused on the challenges of the future: personalized medicine. A key question is to define the role of sign and symptom assessment in an environment in which treatment targets and populations are defined by characteristics that go beyond signs, symptoms and illness course.

Learning Objectives:

- Understand the historic and scientific context in which modern psychometric tools evolved
- Learn how past approaches to measurement issues may apply to new challenges in psychopharmacology

The Hamilton Depression Rating Scale (HDRS) and Brief Psychiatric Rating Scale (BPRS): What Were the Characteristics That Led to Their Success?

Nina R. Schooler, Ph.D.
State University of New York, Downstate Medical Center

The 1960s saw rapid and remarkable development of clinical trials methods in psychopharmacology and rating scales for assessment of psychopathology. The Brief Psychiatric Rating Scale (BPRS) for schizophrenia¹ and the Hamilton Depression Rating Scale (HDRS)² have had remarkable “staying power.” Examination of the history and characteristics of the scales reveals some similarities and differences and provides a useful framework for considering both the early and later history of scale development in these diagnoses. Both instruments were designed for use by clinically experienced assessors and therefore in their original versions provided only limited definitions of anchor points. Items in both instruments rely on relatively global judgments. Both measures have been highly effective in measuring change differentially between treatments. Over time both instruments have been revised, modified and added to by investigators and scale developers while retaining the original names. The origins of the scales were quite different. The HDRS is based on clinical observations and specifically focused on depressed inpatients. The BPRS “items” are named factors derived from a longer and more detailed rating scale. In addition to reviewing strengths and weaknesses of these scales, the presentation will also consider strategies that may contribute to improved scale development in the future.

Learning Objectives:

- Understand the pivotal role of the HDRS and the BPRS in psychopharmacology clinical trials
- Set the stage for consideration of later scale development in schizophrenia and depression

Literature References:

1. Overall JE, et al. The brief psychiatric rating scale. *Psychol Rep* 1962;10:799–812.
2. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56–62.

Panel 9

**Instrumental Moments:
A Historic Overview of Outcome Measure Development in Psychiatric Research
2:15 p.m. – 3:45 p.m.**

Depression Rating Scales and the Development of the Montgomery-Åsberg Depression Rating Scale (MADRS)

Stuart A. Montgomery, M.D.
Imperial College School of Medicine

The evolution of systems for quantifying severity of disorders was, in retrospect, a major advance in the promotion of scientific research in psychiatry replacing the dominant impressionistic culture. For example, the Hamilton Depression Rating Scale (HDRS) was originally developed as a diagnostic scale, but proved extremely useful when it was later adopted as a change scale. However, in the 1970s it became apparent that new measures were needed that could accurately quantify the psychopathology and which were more sensitive to differences in response between treatments. The need for such advanced measures spurred the development of the Montgomery-Åsberg Depression Rating Scale (MADRS).

The methods used to identify the core symptoms of depression were in advance of the current thinking. The items selected for the MADRS were required to be common within different cultures as well as to be sensitive to changes in the severity of the disorder in response to a range of different treatments and in a variety of treatment settings. Sensitivity testing of change scores on individual items and on the total score by comparison with other clinical ratings of severity of depression allowed the scale to be calibrated to the needs of psychopharmacologic research.

Learning Objectives:

- Construction of valid rating instruments
- Measurement of severity in depression

Literature References:

Montgomery SA, et al. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382–89.
Montgomery S. Measures of depression. London: Fulcrum Press; 1978.
Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56–62.

Outcome Measures in Schizophrenia and Psychosis: Past, Present, and Future

Lewis A. Opler, M.D., Ph.D.
Columbia University Medical Center

In 1979, during administration of L-DOPA to inpatients with chronic schizophrenics as part of a research study of tardive dyskinesia, improvement was observed in blunted affect, emotional withdrawal and poor rapport but not in hallucinations or delusions. A study by Strauss, et al. of the concept of positive and negative symptoms provided a theoretical framework for hypothesizing that L-DOPA was ameliorating negative but not positive symptoms. Additional observations suggested that negative symptoms might be treatable using novel pharmacological treatment approaches. In order to measure change in both positive and negative symptoms, the 18 item Brief Psychiatric Rating Scale (BPRS) was supplemented with 12 items from the Psychopathology Rating Schedule (PRS). Originally this supplement was considered as a "special adaptation of the BPRS." However, as new features were introduced (e.g., utilization of both interview and informant information; rating for the past week; new definitions and anchoring points), it became apparent that a new scale had evolved. Reporting on this new scale, the positive and negative symptom scale (PANSS), including its psychometric properties, came at a time when the pharmaceutical industry was looking for a scale that was easily learned and administered, as well as sensitive to change in both positive and negative symptoms.

Learning Objectives:

- Understand why the PANSS was developed
- Understand how the PANSS was developed

Literature References:

Strauss JS, et al. The diagnosis and understanding of schizophrenia, III. Speculations of the processes that underlie schizophrenia symptoms and signs. *Schizophr Bull* 1974;11:61–76.
Kay SR, et al. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261–76.

Panel 10

Recent Advances in Co-Primary Measures of Functional Capacity

4:00 p.m. – 5:30 p.m.

Panel Overview

Richard S.E. Keefe, Ph.D.

Duke University Medical Center

Nina R. Schooler, Ph.D.

State University of New York, Downstate Medical Center

Pivotal trials examining the efficacy of treatments for cognitive impairment in schizophrenia require co-primary measures that reflect ecologically valid assessments of cognitive change. The Validation of Intermediate Measures (VIM) study was sponsored by Measurement and Treatment Research to Improve Cognition in Schizophrenia–Co-Primary and Translation (MATRICS-CT) and supported by the National Institute of Mental Health (NIMH) to examine the psychometric characteristics of several potential co-primary measures. Results from this study have been accepted by the Food and Drug Administration (FDA) representatives. For full functional capacity tests, the University of California, San Diego Performance-Based Skills Assessment (UPSA) was considered the leading test; for short forms, the UPSA and the Test of Adaptive Behavior in Schizophrenia (TABS) were considered the leaders. However, little is known about the characteristics of these measures in clinical trials, particularly in international trials in cultures that differ substantially from North America. The first presenter will present the results from the MATRICS-CT VIM study. The next presenter will describe data from the NIMH Validation of Everyday Real-World Outcomes (VALERO) study that examines the relationship between measures of functional capacity and real-world functioning, a key factor in the determination of whether measures of functional capacity provide relevant data for schizophrenia cognition trials. Next data from industry trials using the UPSA in Eastern Europe and Asia will be presented. The presentations will conclude with comment on the presentations, and there will be a question-and-answer period.

Learning Objectives:

- Understand FDA and MATRICS guidance on co-primary measures for cognition trials in schizophrenia
- Understand latest empirical data on comparison of measures of functional capacity in schizophrenia clinical trials
- Broaden awareness of how current functional capacity measures are utilized in international trials
- Develop clarity on relationship between functional capacity measures and measures of real-world functioning in schizophrenia

Literature References:

- Green MF, et al. Functional co-primary measures for clinical trials in schizophrenia: results from the MATRICS psychometric and standardization study. *Am J Psychiatry* 2008;165:221–28.
- Patterson TL, et al. UCSD performance-based skills assessment: development of a new measure of everyday functioning for severely mentally ill adults. *Schizophren Bull* 2001;27(2):235–45.

Measurement and Treatment Research to Improve Cognition in Schizophrenia – Co-Primary and Translation (MATRICS-CT): Results of Validation of Intermediate Measures Study
Michael F. Green, Ph.D.

David Geffen School of Medicine, University of California, Los Angeles

An obstacle for drug development of cognition-enhancing drugs in schizophrenia is the lack of consensus regarding functionally meaningful co-primary measures. Measurement and Treatment Research to Improve Cognition in Schizophrenia–Co-Primary and Translation (MATRICS-CT) is an industry-government-academic consortium formed to facilitate development of medications for cognitive impairment in schizophrenia. MATRICS-CT conducted the Validation of Intermediate Measures (VIM) study to assess possible co-primary measures.

Clinically stable schizophrenia outpatients were assessed at baseline and at four weeks at four sites. Participants received two types of intermediate measures: performance-based measures of functional capacity and interview-based measures of cognition that were selected through a RAND panel process. Criteria evaluated were: (1) reliability and repeatability; (2) validity correlation with “real-life” functioning and cognitive performance; and (3) practicality and tolerability. The completed study includes 163 patients at baseline and 144 at four weeks. Functional capacity measures met evaluation criteria better than interview-based assessments of cognition. Strengths and weaknesses of each measure will be discussed as these pertain to performance expectations in a psychopharmacology clinical trial. Future steps will be considered.

Learning Objectives:

- Gain knowledge about the process of evaluating potential co-primary measures for use in clinical trials of cognition enhancing drugs
- Gain knowledge about the main results from the VIM study

Literature References:

- Green MF, et al. Functional co-primary measures for clinical trials in schizophrenia: results from the MATRICS psychometric and standardization study. *Am J Psychiatry* 2008;165:221–28.
- Stover EL, et al. New paradigms for treatment development. *Schizophren Bull* 2007;33:1093–99.

Panel 10

Recent Advances in Co-Primary Measures of Functional Capacity

4:00 p.m. – 5:30 p.m.

Assessment of Real World Functional Outcomes: The Validation of Everyday Real-World Outcomes (VALERO) Study

Philip D. Harvey, Ph.D.

Emory University School of Medicine

The Validation of Everyday Real-World Outcomes (VALERO) study is aimed at identification of the optimal procedure to validly measure everyday functioning in schizophrenia. A further goal of the study is to evaluate the accuracy with which different evaluators generate assessments of real-world functioning. Based on the previous findings that ratings of real-world outcomes are often poorly convergent with measures of the patients' ability to perform functional and cognitive skills, the VALERO study examines six different ratings scales for their convergence with the University of California, San Diego Performance-based Skills Assessment (UPSA), the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus cognitive battery, and other performance-based competence measures. The six rating scales selected by a RAND panel for consideration are either social functioning scales (Social Behavior Schedule [SBS] and Social Functioning Scale [SFS]), community functioning scales (Independent Living Skills Survey [ILSS] and Life Skills Profile [LSP]) or hybrids that broadly measure social and independent living outcomes (Quality of Life Scale [QLS] and Specific Levels of Functioning [SLOF]). At the time of this presentation, 200 patients with schizophrenia and an informant will have been rated on these six scales and have completed the performance-based assessment battery. The scales, or elements of the scales, that are found to be maximally convergent will be presented in detail; the information from this part of the study should help to identify better ways to rate real-world functioning in people with schizophrenia.

Learning Objectives:

- Understand the correlation between real world outcomes and performance-based functional assessment
- Understand the best performing real-world functioning scale

Literature References:

Feea R, et al. Validating measures of real-world outcome: The results of the VALERO expert survey and RAND appropriateness panel. *Schizophr Bulletin*. Forthcoming.
 Bowie CR, et al. Self-assessment of functional status in schizophrenia. *J Psychiatr Res* 2007;41:1012–18.

Recent Advances in Co-Primary Measures of Functional Capacity

Kolleen H. Fox, Ph.D.

NeuroCog Trials, Inc.

Following the recommendations of the Food and Drug Administration (FDA), pharmaceutical companies interested in developing a drug to enhance cognition in patients with schizophrenia have been tasked with demonstrating change on both traditional measures of cognition and co-primary measures of functional capacity. The University of California, San Diego (UCSD) Performance-based Skills Assessment (UPSA-2) and UPSA-Brief have been implemented as co-primary measures in cognition studies of schizophrenia drugs for several years. It is widely accepted that these measures offer the best psychometric qualities of tests in their class. However, most of the data regarding these measures to date has been collected in the United States with an English-speaking patient population. Less is known about how the UPSA-2 and UPSA-B perform in studies conducted outside the United States. Very recently, the UPSA-Brief has been translated into 15 languages for use in eight countries in two separate trials. This presentation will focus on the implementation of the UPSA-B in trials in European and Asian countries, including the translation process, cultural considerations, and preliminary results. Directions for further study will also be discussed.

Learning Objectives:

- Learn about the current state of co-primary measures of functional skills in clinical trials of schizophrenia
- Learn about the challenges of implementing co-primary measures in foreign countries

Literature References:

Green MF, et al. Functional co-primary measures for clinical trials in schizophrenia: results from the MATRICS psychometric and standardization study. *Am J Psychiatry*. Forthcoming.
 Harvey PD, et al. Performance-based measures of functional skills: Usefulness in clinical treatment studies. *Schizophr Bull* 2007;33:1138–48.
 Patterson TL, et al. UCSD performance-based skills assessment: development of a new measure of everyday functioning for severely mentally ill adults. *Schizophr Bull* 2001;27:235–45.

Panel 11

Geriatric Psychopharmacology: New Directions, Challenges, and Opportunities for the Future

4:00 p.m. – 5:30 p.m.

Panel Overview

Jovier D. Evans, Ph.D.

National Institute of Mental Health

Given the approaching avalanche of geriatric mental health needs, the National Institute of Mental Health (NIMH) Geriatrics Research Branch must continue to look for novel treatment development and individualized approaches to expand the treatment benefits for the elderly. In addition, new advances in clinical neuroscience have pushed for the identification of biomarkers and correlates of treatment response variability. The goal then becomes how best to integrate these mechanistic questions into treatment research. The purpose of the present panel discussion will be to highlight new and interesting work in the area of geriatric clinical research that may point to the development of novel biomarkers or treatment moderators that could be included in new clinical intervention studies. A secondary goal of the panel discussion will be to highlight areas of interest for the Geriatrics Research Branch to the audience. Topics will include: (1) imaging studies of elders with late life generalized anxiety disorder as it relates to treatment response; (2) investigations of molecular imaging among elders with comorbid Diabetes and Major Depressive Disorder; and (3) examining moderators of treatment response in older adults with Bipolar Disorder. New and emerging investigators in the fields of clinical psychology, pharmacotherapy and neuroimaging in late-life neuropsychiatric disorders will highlight the role of translational research and the use of these techniques for the development and advancement of clinical practice.

Learning Objectives:

- Discuss the priorities and interests of the NIMH Geriatrics Research Branch
- Highlight neural markers of treatment response in late life generalized anxiety disorder
- Examine neurobiological signatures of patients with late life major depressive disorder
- Examine and discuss moderators of treatment success among elders with bipolar disorder

Neural Markers of Treatment Response in Late-Life Generalized Anxiety Disorder

Carmen Andreescu, M.D.

University of Pittsburgh School of Medicine

Generalized anxiety disorder (GAD) is highly prevalent in the elderly and is associated with poorer quality of life, cognitive impairment and increased health care utilization.¹ Moreover, treatment response is poor and variable and probably related to age-induced neurobiological changes.² The identification of the late-life GAD neurobiological profiles of treatment response would allow for the further design of more efficacious and more personalized treatment strategies.² Recent data describe the reciprocal connection between amygdala and rostral anterior cingulate cortex (rACC) in modulation of anxiety.³ Pretreatment rACC-amygdala responsivity has been reported to correlate with magnitude of treatment response to selective serotonin reuptake inhibitors (SSRI) in midlife GAD.⁴ Amygdala and ventromedial prefrontal cortex (vmPFC) have been inversely coupled during regulation of negative affect in elderly healthy subjects.³ Aging is associated with impaired structural and functional connectivity, which can play a role in both persistence of anxiety symptoms (e.g., through disruption of fear-extinction neurocircuitry) and in the observed poorer response to treatment of late-life GAD.³ Previous studies in midlife GAD subjects have indicated that the activity in the amygdala-rACC axis is a useful predictor of venlafaxine treatment response.⁴ We present preliminary data suggesting (1) an increased activation in amygdala, insula and rACC in late life GAD; (2) the role of the limbic-prefrontal network in worry modulation. We also discuss age-related vascular and degenerative changes in the limbic-prefrontal network and their correlation with treatment response in late-life GAD.

Learning Objectives:

- Learn about the neural basis of late life GAD
- Consider structural and functional neuroimaging changes in late life GAD
- Consider neural markers of treatment response in late life GAD

Literature References:

1. Andreescu C, et al. Generalized anxiety disorder severity scale validation in older adults. *Am J Geriatr Psychiatry* 2008;16(10):813–18.
2. Lenze EJ, et al. Bringing the bedside to the bench, and then to the community: a prospectus for intervention research in late-life anxiety disorders. *Int J Geriatr Psychiatry* 2009;24(1):1–14.
3. Urry HL, et al. Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. *J Neurosci* 2006;26(16):4415–25.
4. Whalen PJ, et al. A functional magnetic resonance imaging predictor of treatment response to venlafaxine in generalized anxiety disorder. *Biol Psychiatry* 2008;63:858–63.

Panel 11

Geriatric Psychopharmacology: New Directions, Challenges, and Opportunities for the Future
4:00 p.m. – 5:30 p.m.

Neuroanatomical and Neurochemical Sequelae of Major Depression and Type 2 Diabetes

Olu A. Ajilore, M.D., Ph.D.
University of Illinois, Chicago

Type 2 diabetes and major depression are disorders that are mutual risk factors and may share similar pathophysiological mechanisms. To further understand these shared mechanisms, we examined the biochemical basis of depression in patients with type 2 diabetes using proton magnetic resonance spectroscopy. Brain regions that are thought to be involved in the pathophysiology of major depression were studied in patients with type 2 diabetes and major depression, as well as type 2 diabetes alone, compared to healthy controls. We examined if there were any abnormalities in brain metabolites that were specific for diabetes or major depression in these regions. We found that in diabetic subjects (with or without major depression), there was elevated myo-inositol in frontal white matter which may indicate injury reflected as gliosis. We also found elevated glutamate in subcortical regions of depressed diabetic subjects. Abnormal glutamate has been seen in other spectroscopy subjects with major depression, suggesting that it is an important neurotransmitter in the pathophysiology of major depression. The changes in myo-inositol noted in diabetic subjects were also significantly correlated with neuropsychological performance, suggestive of a functional link between these metabolic changes and cognition associated with diabetes and depression.

Learning Objectives:

- Understand that type 2 diabetes and major depression are mutual risk factors
- Understand that magnetic resonance spectroscopy can be used to detect biochemical abnormalities associated with type 2 diabetes and major depression
- Understand the neuroanatomical changes associated with major depression and type 2 diabetes

Literature References:

Ajilore, et al. Measurement of brain metabolites in patients with type 2 diabetes and major depression using proton magnetic resonance spectroscopy. *Neuropsychopharmacology* 2007 Jun;32(6):1224–31.
Kumar, et al. Gray matter prefrontal changes in type 2 diabetes detected using MRI. *J Magn Reson Imaging* 2008 Jan;27(1):14–9.

Clinical Course and Moderators of Treatment Response in Late-Life Bipolar Disorder

Colin A. Depp, Ph.D.
University of California, San Diego School of Medicine

Late life bipolar disorder is poorly understood. This presentation describes the current understanding of the clinical course of bipolar disorder in older adults, focusing on clinically important modifiers of treatment outcome and non-pharmacological strategies to address these modifiers. Cognitive impairments and medical comorbidities have substantial impact on functional capacities such as medication adherence. We provide an overview of the magnitude and course of cognitive deficits associated with bipolar disorder, which may exhibit greater decline and within-person variability into later life compared with other late life psychiatric disorders. Older adults with bipolar disorder are also at high risk for cardiometabolic illnesses, often adding to already complex medication regimens. The relationship between cognitive deficits and functional outcomes is mediated by functional capacity, with evidence suggesting that diminished medication management ability creates greater risk for unintentional non-adherence. On balance, some self-management behaviors may improve over the course of the illness as indicated by qualitative data. Skills-based non-pharmacological interventions are effective in rehabilitation of other late-life severe mental illnesses, and we present preliminary data from two interventions designed to compensate for the negative impact of cognitive deficits on functioning. The first is a group intervention aimed at improving medication management abilities to enhance adherence. The second uses mobile technology to cue patients to engage in self-management behaviors based on ongoing monitoring. We conclude with directions for future research.

Learning Objectives:

- Identify the course of late life bipolar disorder
- Specify the role of cognitive deficits on functional capacities in late life bipolar disorder
- Review non-pharmacological approaches to enhancing outcomes in late life bipolar disorder

Literature References:

Depp C, et al. Bipolar disorder in older adults: a critical review. *Bipolar Disord* 2004;6:343–67.
Depp C, et al. Assessment of medication management ability in middle-aged and older adults with bipolar disorder. *J Clin Psychopharmacol* 2008;28:225–9.

Panel 11

Geriatric Psychopharmacology: New Directions, Challenges, and Opportunities for the Future

4:00 p.m. – 5:30 p.m.

NIMH Update: Priorities in Geriatric Intervention Research

Jovier D. Evans, Ph.D.

National Institute of Mental Health

National Institute of Mental Health (NIMH) program staff with aging-related portfolios will describe the current priorities for the Institute, inform participants of NIMH programs that support research efforts on aging and mental health and outline specific opportunities for new studies. With the new NIMH Strategic Plan, clinical research paradigms will need to shift to become more individualized and reflect treatment development approaches that would transform clinical research efforts. Aging-related issues ranging from clinical neuroscience to community-related effectiveness research will be discussed as opportunities for innovation and discovery. In addition, this panel will describe what researchers planning to seek grant funding from National Institutes of Health (NIH) need to know about significant changes affecting the submission process for all NIH grant applications.

Learning Objectives:

- Know the current research priorities being supported by NIMH
- Discuss future research directions and strategies for the field of geriatric psychopharmacology research

Literature References:

- National Institute of Mental Health: National Institute of Mental Health strategic plan. Bethesda, MD: NIH Publication; 2008.
- Insel TR. Translating scientific opportunity into public health impact: a strategic plan for research on mental illness. *Arch Gen Psychiatry* 2009;66:128–133.
- Smith GS, et al. Translational research in late-life mood disorders: implications for future intervention and prevention research. *Neuropsychopharmacol* 2007;32:1857–75.



Plenary Session III

Food and Drug Administration Symposium

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

Symposium Overview

Thomas P. Laughren, M.D.
Food and Drug Administration

This session will include talks covering several different topics of current interest and activity both in the Division of Psychiatry Products and at the Food and Drug Administration (FDA) generally. Thomas Laughren from the Division of Psychiatry Products will briefly review the last few decades of Psychopharmacological Drug Development at FDA and then discuss what can be expected from FDA in future years. Other speakers will expand on several of the themes introduced by Dr. Laughren. Joga Gobburu, from the Division of Pharmacometrics in the Office of Clinical Pharmacology at FDA, will discuss the role of end-of-phase 2A meetings with FDA in drug development. Jonathan Levine from the Office of Critical Path Programs will give an overview of current approaches to establishing data standards for data submitted to FDA. Laurie Duncan from the Division of Psychiatry Products will talk about the evolving Sentinel Initiative at FDA and how this can be expected to assist in our efforts to understand the risks of marketed drugs. Salma Lemtouni from the Office of the Center Director will provide an overview of the Safe Use Initiative at FDA and discuss how FDA intends to be proactive in ensuring that drugs are used safely in the community.

Learning Objectives:

- Understand the history of psychopharmacological drug development and what might be expected in the future from FDA
- Understand the role of end-of-phase 2A meetings with FDA in drug development
- Develop some understanding of current approaches to establishing data standards for data submitted to FDA
- Understand the evolving Sentinel Initiative at FDA
- Understand the Safe Use Initiative at FDA

