



**LEARNING FROM THE PAST TO ADVANCE
THE FUTURE OF MENTAL HEALTH TREATMENT**

LATE-BREAKING RESEARCH REPORTS

50TH ANNIVERSARY MEETING

June 14 - 17, 2010

Boca Raton Hotel

Boca Raton, FL

Late-Breaking Research Reports

10:45 a.m. – 12:15 p.m.

A Two-Year Randomized Clinical Trial of Long-Acting Injectable Risperidone and Oral Antipsychotics in Unstable Chronic Schizophrenia

Robert Rosenheck, M.D.
Yale Medical School and Veteran Affairs, West Haven Healthcare System

Background: Medication non-adherence is a major reason for poor outcomes in schizophrenia. Long-acting injectable (LAI) risperidone microspheres, the first LAI second generation antipsychotic (SGA), may improve adherence and thereby outcomes, but has not been tested in a long-term randomized trial of unstable patients, against flexibly prescribed oral treatment.

Methods: Patients with schizophrenia or schizo-affective disorder who had been hospitalized within the past two years, or judged to be at risk of hospitalization because of increasing psychiatric service use, were randomly assigned to LAI risperidone bi-weekly 12.5–50 mg/injection, or to the psychiatrist's choice of oral antipsychotics (N=369). The primary intention-to-treat endpoint, psychiatric hospitalization, was documented with Department of Veterans Affairs administrative data, supplemental patient interviews, and review of discharge summaries from non-VA admissions. Symptoms and quality of life were assessed through blinded video-conference interviews. The duration of the trial after assignment was two years.

Results: Most patients were hospitalized either at randomization, or within the previous two years, or were at current risk. Most participants also acknowledged problems with medication adherence, and with alcohol or drug use. Over two years, we have determined whether LAI risperidone showed any difference over oral anti-psychotics (virtually all SGAs) on time to first psychiatric hospitalization or time to all cause discontinuation of randomized treatment. Mixed models using up to 18 months of data have evaluated the significance of any advantage of LAI risperidone on measures of psychiatric symptoms, quality of life, substance abuse, neurological side effects, weight gain or reduction of health services use.

Conclusions: This study, lasting over two years, has assessed whether LAI risperidone shows superiority to psychiatrist's choice of oral treatment in patients with schizophrenia at relatively high risk of hospitalization. This will be the first public presentation of the results.

- Learning Objectives:**
- Evaluate long-acting risperidone and oral medications
 - Demonstrate comparative effectiveness methods

Literature References:
Fleischhacker WW, et al. Treatment of schizophrenia with long-acting injectable risperidone: a 12-month open-label trial of the first long-acting second-generation antipsychotic. *J Clin Psychiatry* 2003;64(10):1250–7.
Kane JM, et al. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiatry* 2003 June;160(6):1125–32.

Feasibility and Pilot Efficacy Results from the Multi-Site Cognitive Remediation in the Schizophrenia Trials Network (CRSTN) Study

Richard Keefe, Ph.D.
Duke University Medical Center

Background: Cognitive remediation holds promise for schizophrenia treatment, but results have been variable and few multi-site studies have been completed.

Methods: Patients from nine sites were randomized to either “treatment” condition consisting of the PositScience auditory training program with weekly NEAR ‘bridging groups’ or a ‘control’ condition that involved computer games and weekly healthy lifestyles groups. Patients were expected to complete three to five one-hour sessions per week for 40 sessions or 12 weeks, whichever came first.

Results: The primary outcomes for this project were feasibility results. Within the three month enrollment period, 53 were enrolled and 47 met criteria for study completion. Thirty-one patients completed 40 sessions, and 16 patients completed fewer than 40 sessions in 12 weeks of treatment. The exploratory treatment outcomes were Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MCCB) improvement at the end of treatment and after 20 weeks of treatment. After 20 weeks, patients receiving the treatment condition had MCCB composite scores adjusted for baseline of 32.7 compared to 29.0 for control patients (F=4.16, df=1,46, p=0.047). At the end of treatment, patients receiving the treatment condition had MCCB composite scores adjusted for baseline of 32.4 compared to 29.7 for those receiving the control condition (F=2.26, df=1,47, p=0.14). Post hoc analyses suggested that the MCCB domains contributing most strongly to improvement in the treatment group were verbal learning, social cognition (p’s<0.05) and reasoning and problem-solving (p<0.10).

Discussion: Multi-site trials of cognitive remediation using the PositScience auditory training program with the NEAR method of weekly bridging groups appear feasible, and the effect sizes for cognitive improvement are consistent with potential significant benefit in well-powered studies.

- Learning Objectives:**
- Understand the crucial issues about the efficacy of cognitive remediation for patients with schizophrenia
 - Understand the key methodological issues and feasibility of implementing multi-site cognitive Akinnusi remediation trials

Literary References:
Keefe RSE, et al. Report from the working group conference on multi-site trial design for cognitive remediation in schizophrenia. *Schizophren Bull* 2010; doi 10.1093/schbul/sub010 [Epub ahead of print].
Fisher M, et al. Using neuroplasticity-based auditory training to improve verbal memory in Schizophrenia. *Am J Psychiatry* 2009;166:805–11.

Late-Breaking Research Reports

10:45 a.m. – 12:15 p.m.

A Six-Week Randomized Double-Blind Placebo-Controlled Trial of Ziprasidone for the Acute Depressive Mixed State

Nassir Ghaemi, M.D., M.P.H.
Tufts Medical Center

Objective: To examine the efficacy of ziprasidone versus placebo for the depressive mixed state in patients with bipolar II disorder or unipolar depression.

Methods: Seventy-two patients with bipolar disorder type II or major depressive disorder were randomized in a double-blind, placebo-controlled study to ziprasidone (40–160 mg/d) or placebo for six weeks. They met DSM-IV criteria for a major depressive episode, while also meeting two or three (but not more or less) DSM-IV manic criteria. They did not meet DSM-IV criteria for a mixed or manic episode. Baseline psychotropic drugs were continued unchanged. Primary endpoint measured the change in baseline Montgomery-Åsberg Depression Rating Scale (MADRS). The mean dose of ziprasidone was 129.7 ± 45.3 mg/day.

Results: General linear model employing repeated measures ANOVA showed a significant reduction in MADRS scores from baseline to end of treatment with ziprasidone (baseline MADRS = 23.12 ± 6.29 , end of treatment MADRS = 12.02 ± 10.86) versus placebo (baseline MADRS 24.7 ± 8.02 , end of treatment MADRS 18.38 ± 9.42) ($F=8.273$, $p<0.0006$). Efficacy was more pronounced with monotherapy (change in MADRS = 9.09 ± 10.4) versus adjunctive therapy (change in MADRS = 0.97 ± 10.6 ; ANOVA, $F=2.52$, $p=0.09$). Overall ziprasidone was well tolerated, without notable worsening of weight or extrapyramidal symptoms.

Learning Objectives:

- Learn that ziprasidone was proven effective and relatively tolerable in this first randomized controlled trial of any medication for the depressive mixed state
- Understand that these results provide preliminary support for both the nosological validity and the practical utility of a broadening of the concept of mixed mood episodes

Literature References:

- Koukopoulos A, et al. Agitated depression as a mixed state and the problem of melancholia. *Psychiatry Clin North Am* 1999;22(3):547–64.
- Swann AC. Depression, mania, and feeling bad: the role of dysphoria in mixed states. *Bipolar Disord* 2000;2(4):325–7.

Deep Brain Stimulation for Treatment Resistant Major Depression: Can We Have a Personalized Approach? Intraoperative Responses During Programming and Long Term Outcome

Cristina Cusin, M.D.
Massachusetts General Hospital, Harvard Medical School

Background: The use of deep brain stimulation (DBS) in psychiatry is an exciting new frontier for neuroscientists and our group is currently involved in a double-blind randomized clinical trial for deep brain stimulation at the ventral capsule/ventral striatum (VC/VS) site for severe treatment-resistant major depression disorder (MDD). The choice of stimulation parameters for each patient derives from the experience in treating movement disorders with DBS, and it is based on the presence of acute effects and lack of adverse events. Very little is known about the correlation between those acute effects and long term outcome.

Methods: Ten total DBS leads in five patients with chronic and severe treatment-refractory MDD were tested during the surgery with monopolar stimulation. Patients were part of a previously published sample.¹

Results: Ninety-four single-blinded intraoperative stimulations were performed. Seventeen were at 0V (sham), and in only two of those, the patients did report effects, while in 17 out of 77 stimulation test at voltage between 2V and 8V, patients presented positive (happiness, laughter) or negative (twitching, chest tightness, warmth) effects. Over the course of two years, in four out of five cases the stimulation was maintained monopolar, while in one case it was changed to bipolar. The voltage was progressively increased in all patients to the 8V–10V range. The absence of intraoperative acute mood improvement was not correlated with the antidepressant response at 12 months, and vice versa the presence of smiling and laughing during acute stimulation did not predict response at 12 months.

Learning Objectives:

- Recognize the challenges of designing and conducting a trial involving a device are significantly different from those of a trial involving medications
- Understand the similar challenges are present in effectiveness studies, and a personalized approach could be implemented in psychopharmacology studies

Literature References:

1. Malone DA Jr, et al. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol Psychiatry* 2009;65(4):267–75.
2. Tye SJ, Frye MA, Lee KH. Disrupting disordered neurocircuitry: treating refractory psychiatric illness with neuromodulation. *Mayo Clin Proc* 2009;84(6):522–32.

Effects of Modafinil on Psychopathology, Daytime Sleepiness and Motor Symptoms in Schizophrenia

James B. Lohr, M.D.

Veteran Affairs, San Diego Healthcare System

Modafinil, as an agent with demonstrated neuronal effects, particularly within the frontal lobes, may be a drug with therapeutic benefits on negative and parkinsonian symptoms and signs in schizophrenia. In addition, its efficacy in narcolepsy suggests that it may be helpful in patients with schizophrenia who also have excessive daytime sleepiness (EDS), a fairly common problem in the schizophrenia population. We assessed the potential efficacy of modafinil on these three constellations of symptoms—negative, EDS and parkinsonian. Twenty-four males with schizophrenia or schizoaffective disorder (ages 20 to 63) and prominent negative symptoms (Positive and Negative Syndrome Scale [PANSS], negative subscale score >20) were randomly assigned to adjunctive treatment with modafinil (titrated from 50 mg/day to 200 mg/day) or placebo for eight weeks. Subjects were stratified by EDS status (Epworth Sleepiness Scale [ESS] score >nine). Negative symptoms and parkinsonism were assessed using the PANSS and Simpson-Angus Scale (SAS) respectively.

Using repeated measures ANOVA, there were no significant effects of modafinil on negative symptoms or EDS, consistent with previous studies demonstrating little effect of modafinil on negative symptoms in schizophrenia. However there was a significant decrease in parkinsonian signs with the modafinil group showing a 43% reduction over eight weeks compared to only a 3% decrease in the placebo group. The significant reduction found in parkinsonism suggests that modafinil may have therapeutic potential in patients with antipsychotic-induced parkinsonism and possibly parkinsonism due to other causes.

Learning Objectives:

- Explore potential effects of modafinil in psychotic illness
- Explore potential effects of modafinil on motor symptoms

Literature References:

Ballon JS, et al. A systematic review of modafinil: potential clinical uses and mechanisms of action. *J Clin Psychiatry* 2006;67(4):554–66.
Farrow TF, et al. Modafinil and unconstrained motor activity in schizophrenia: double-blind crossover placebo-controlled trial. *Br J Psychiatry* 2006;189:461–2.



Late-Breaking Research Reports

2:15 p.m. – 3:45 p.m.

The Incremental Benefit and Cost of Coordinated Anxiety Learning and Management (CALM) for Anxiety Treatment in Primary Care**Jutta M. Joesch, Ph.D.**

University of Washington School of Medicine

Background: Improving the quality of mental health care requires integrating successful research interventions into “real world” practice settings. Coordinated Anxiety Learning and Management (CALM) is a flexible treatment-delivery model for primary care that targets four common anxiety disorders. Recently, CALM was found to be superior to usual care (UC) in improving anxiety symptoms, functional disability and the quality of anxiety care.

Objective: To estimate the incremental benefit, incremental cost and incremental net benefit of CALM versus UC.

Methods: A randomized trial conducted from June 2006 to October 2009 comparing CALM with UC in 17 primary care clinics in four U.S. cities. One thousand-four patients with panic, generalized anxiety, social anxiety and/or post traumatic stress disorder, with or without major depression, age 18–75 and English- or Spanish-speaking received treatment for up to 12 months. Blinded follow-up assessments at six, 12 and 18 months after baseline were completed.

Anxiety-free days (AFD) from baseline to 18-month follow-up were estimated based on 12-item Brief Symptom Inventory scores. For the same period, expenditures for outpatient clinic and emergency room (ER) visits were estimated using participant-reported health care use and per visit expenditure information from the Medical Expenditure Panel Survey.

Results: Over 18 months, CALM participants, on average, had 56 additional AFD (95% CI, +31 to +80) and \$511 additional expenses for outpatient clinic and ER visits (95% CI: \$189 lower to \$1210 higher). The incremental net benefit was positive, if an anxiety-free day is valued at \$30 or higher.

Conclusions: Compared with UC, CALM has significant clinical benefit with a modest increase in expenditures for outpatient clinic and ER visits.

Learning Objectives:

- Understand the concepts of incremental benefit, incremental cost and incremental net benefit (INB)
- Recognize their application to and results for CALM

Literature References:

Roy-Byrne P, et al. Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomized effectiveness trial. *JAMA*. Forthcoming.

Simon GE, et al. Incremental benefit and cost of telephone care management and telephone psychotherapy for depression in primary care. *Arch Gen Psychiatry* 2009;66(10):108.

A Comparison of Prolonged Exposure and Sertraline for Post Traumatic Stress Disorder (PTSD): Acute Outcomes and Treatment Preferences**Norah C. Feeny, Ph.D.**

Case Western Reserve University

In post traumatic stress disorder (PTSD), there have been no large scale clinical trials directly comparing a well-validated cognitive behavioral therapy and a selective serotonin reuptake inhibitor (SSRI). The present study examines treatment preferences and acute outcome comparing prolonged exposure (PE) and sertraline (SER) in the treatment of 200 men and women with chronic PTSD. Utilizing a doubly randomized preference trial design, participants were first randomized to choice or no choice between PE and SER, and then those in the no choice arm were re-randomized to either PE or SER. Prior to randomization, participants view detailed, counterbalanced videotaped treatment rationales of both PE and SER. After viewing these rationales, participants were asked for their treatment preference. Across all participants, the majority preferred PE over SER. Following randomization, participants received either 10 weeks of PE or SER, after which responder status was determined. Participants were followed-up at three, six, 12 and 24 months. We will present outcome results from the acute phase of treatment. Overall, although results suggest that PE and SER are both efficacious, they also highlight the presence of clear treatment preferences for PTSD and their potential impact on outcome. Our results underscore the importance of understanding patient preferences and encourage a rethinking of one-size fits all approaches to treatment for PTSD.

Learning Objectives:

- Learn about the short-term efficacy of PE and SER for PTSD
- Learn about treatment preferences for PTSD

Literature References:

Zoellner LA, et al. What you believe is what you want: modeling treatment preferences for PTSD. *J Behav Ther Experimental Psychiatry* 2009;40:455–67.

Feeny NC, et al. What would you choose? sertraline or prolonged exposure for chronic PTSD. *Depression Anxiety* 2009;26:724-31.

Late-Breaking Research Reports

2:15 p.m. – 3:45 p.m.

The Importance of Sustained Consent in Clinical Trials in Schizophrenia: Evidence of Continuing Capacity to Consent

Bernard A. Fischer, M.D.
University of Maryland School of Medicine

Ethical research requires that subjects maintain some study knowledge during participation. It is unclear what elements of informed consent are lost over the course of a clinical trial in schizophrenia and when they are lost. To address this issue, we followed participants with schizophrenia enrolled in real clinical trials of >8 weeks and assessed their capacity to consent at set time points using the modified Evaluation to Sign Consent (mESC; max score=92). Participants reviewed the medication trial consent form and received a baseline mESC and Brief Psychiatric Rating Scale (BPRS) at Week 0 of the medication study. They were then randomized to receive a follow-up mESC and BPRS at one, four and eight weeks; four and eight weeks; or only at eight weeks. Fifty-nine subjects were enrolled with a mean age of 43.2+10.6 years. Participants were 64% male, 40% non-white and had 12.4+2.2 years education. Baseline BPRS total was 33.2+7.6; baseline mESC total was 86.9+10.9. Over eight weeks, there were no meaningful changes in mESC scores (Week 1: 88.5+11.8, Week 4: 86.1+11.1, Week 8: 86.4+13.2). BPRS totals did not correlate to mESC scores at any time point.

Learning Objectives:

- Identify the elements of informed consent
- Understand the importance of sustained consent during clinical trials
- Review the evidence (presented above) that people with schizophrenia can complete clinical trials of up to eight weeks with little change in baseline capacity to consent

Literature References:

Prentice KJ, et al. Maintaining informed consent validity during lengthy research protocols. *IRB: Ethics Human Res* 2007;29(6):1–6.
Dunn LB. Capacity to consent to research in schizophrenia: the expanding evidence base. *Behav Sci Law* 2006;24(4):431–45.

Long-Acting Injectable Medication Maintenance Treatment of “First-Episode” Schizophrenia—A Randomized Effectiveness Study

Peter J. Weiden, M.D.
University of Illinois, Chicago

Objective: Long acting antipsychotic medications (LAI) are often considered the most effective approach to long-term maintenance treatment of schizophrenia. Because LAI tends to be reserved for persistently ill, chronic patients, little is known about the effectiveness of this approach in recently diagnosed, “first-episode” schizophrenia patients just beginning maintenance antipsychotic treatment.

Methods: A prospective randomized controlled trial (RCT) conducted from December 2004-March 2007 enrolled “first-episode” patients defined by appropriate Structured Clinical Interview for DSM Disorders (SCID) diagnosis and ≤16 weeks lifetime antipsychotic exposure. Participants were randomized (2:1 ratio) to recommendation of risperidone long-acting injectable (RLAI) or continuing on oral therapy (ORAL). Nonadherence behavior was defined as a medication gap =14 days. Adherence attitudes were ascertained blindly with the Rating of Medication Influences (ROMI). Analysis defined treatment groups by intent-to-treat (ITT) and as-actually-treated (AAT).

Results: Most patients stopped their medication. There are significant adherence benefits for RLAI acceptors within three months that were not sustained. However, the few patients who stayed adherent after 52 weeks were all treated with LAI, and patients who stopped RLAI beforehand often resumed LAI treatment after relapse. Overall adherence attitudes on ROMI did not differ between groups.

Conclusions: Most first-episode patients who accept oral antipsychotic will accept a recommendation of LAI. Many patients who discontinue LAI continue to accept LAI after a relapse. These results support the feasibility and acceptability of LAI intervention shortly once a diagnosis of schizophrenia is established after the first psychotic episode.

Learning Objectives:

- Present new data on medication adherence outcomes for up to two years follow-up in recently diagnosed “first-episode” schizophrenia patients starting outpatient maintenance antipsychotic
- Compare the effectiveness of a LAI approach versus continuing on oral antipsychotic therapy on adherence outcomes for up to two-year follow-up
- Present data on feasibility and acceptance of LAI shortly after a diagnosis of schizophrenia is made, including acceptance of initial recommend, duration of time on LAI, impact on adherence attitudes and re-acceptance of LAI after discontinuation and relapse

Literature References:

Weiden PJ, et al. A randomized controlled trial of long-acting injectable risperidone versus continuation on oral atypical antipsychotics for first-episode schizophrenia patients: initial adherence outcome. *J Clin Psychiatry* 2009;70(10):1397–406.
Velligan DI, et al. The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness. *J Clin Psychiatry* 2009;70 Suppl 4:1–46.
Weiden PJ, et al. Rating of medication influences (ROMI) scale in schizophrenia. *Schizophr Bull* 1994;20:297–310.

Late-Breaking Research Reports

2:15 p.m. – 3:45 p.m.

Methylphenidate as a Potential Treatment for Apathy in Alzheimer's Disease (AD)

Jacobo Mintzer, M.D., M.B.A.
Medical University of South Carolina

Apathy in the context of Alzheimer's disease (AD) constitutes a major clinical and public health problem with serious adverse consequences for patients and caregivers. Patients suffering from apathy experience decreased motivation, relying heavily on caregivers to initiate and oversee daily activities. Apathetic patients are more likely to require institutionalization, the largest single driver of direct costs in AD. Apathy is one of the most common neuropsychiatric symptoms (NPS) of AD, affecting approximately 70% of AD patients.

We have recently received funding from the National Institutes of Health to conduct a study on the safety and efficacy of methylphenidate as a potential treatment for apathy in AD. Funding was granted on the basis of three preliminary studies: (1) SPECT imaging showing evidence of disruption of perfusion in areas related to the dopaminergic reward system in AD patients suffering from apathy, when compared with equally impaired patients without these symptoms; (2) a challenge study showing a blunted response to dextroamphetamine challenge in AD patients suffering from apathy, when compared with a similar population without these symptoms; and (3) a small pilot crossover study showing a possible effect of methylphenidate in the treatment of these patients. Overall, patients demonstrated greater improvement with methylphenidate compared to placebo according to Apathy Evaluation Score total change scores (end of treatment–baseline; Wilcoxon $Z=-2.00$, $p=0.047$). Although these data have been published previously, this is the first time that data will be structured to support the dopaminergic hypothesis.

Learning Objectives:

- Understand the research leading to the hypothesis supporting a dopaminergic deficit in individuals suffering from apathy in AD
- Understand the neuroimaging challenge and clinical trial preliminary work that supports this hypothesis and leads to the execution of a large double-blind study

Literature References:

- Mega M, et al. The spectrum of behavioral changes in Alzheimer's disease. *Neurology* 1996;46: 130–35.
- Reimherr F, et al. A double-blind, placebo-controlled, crossover study of osmotic release oral system methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. *J Clin Psychiatry* 2007;68:93–101.
- Tremblay LK, et al. Probing brain reward system function in major depressive disorder: altered response to dextroamphetamine. *Arch Gen Psychiatry* 2002;59:409–16.



Treatment of Adults with Attention Deficit Hyperactivity Disorder (ADHD): Cognitive Behavioral Therapy (CBT) Only Versus Medication and CBT

Lily Hechtman, M.D., F.R.C.P.
McGill University Health Center

Objectives: To evaluate the relative efficacy of cognitive behavior therapy (CBT) only versus medication and CBT combined for adults with attention deficit hyperactivity disorder (ADHD).

Background: Epidemiological studies of 10,000 subjects¹ have shown that 4.4% of the general population may have ADHD. ADHD in Adults is associated with significant impairment in occupational, social, and emotional functioning and high rates of axis I and II comorbidity.² However, only 10% receive comprehensive assessments and treatment.¹ One reason for this very low rate of diagnosis and treatment is the scarcity of clinical expertise and thus available clinical services. The treatment studies that do exist have mainly focused on medication treatment which addresses ADHD symptoms but not functioning. “Pills don’t teach skills,” and thus for many functional outcomes even with medication, treatment remains sub-optimal. This study is one of the few which looks at both medication and cognitive behavioral therapy in addressing symptoms and functioning in this population. Therefore, presentation of this study will hopefully point out the need for interventions which help functioning and thus inform evidence based treatment guidelines.

Methods: Sixty adults with ADHD were randomly assigned to receive either a 12-week group CBT program or medication with CBT combined. The CBT program, with six to 10 subjects per group, addressed organizational and time management skills, anger management and relationships, as well as self-esteem and cognitive restructuring issues. Individual coaching calls twice a week were also part of this program. Outcome evaluations included ADHD symptoms and the areas outlined above which were targeted in the CBT program.

Results: The combined group benefited most from the CBT program.

Conclusions: Adults with ADHD may require both medication and CBT for optimal outcome.

Learning Objectives:

- Describe the limitations of medication treatment for adults with ADHD regarding functional outcomes
- Describe a cognitive behavioral therapy program designed to address some of these functional outcomes
- Outline the results of combining medication and CBT for the treatment of adults with ADHD

Literature References:

1. Kessler RC, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry* 2006;163:716–23.
2. Cumyn L, et al. Comorbidity in adults with attention-deficit/hyperactivity disorder. *Can J Psychiatry* 2009 Oct;54(10):673–83.

Metformin in the Treatment of Antipsychotic-Induced Weight Gain in Schizophrenia

Fredrik Jarskog, M.D.
New York State Psychiatric Institute, Columbia University

Background: Antipsychotic medications have been associated with weight gain and many patients struggle with obesity, dyslipidemia and diabetes.^{1,2} Given the difficulty of achieving lasting weight loss from behavioral interventions alone, many adjunctive pharmacological interventions have been considered.³ Metformin is a safe and well-tolerated biguanide antihyperglycemic drug associated with modest weight loss in patients with type II diabetes mellitus. A recent study found that metformin can produce weight loss in patients with first-episode schizophrenia who had gained 10% of baseline body weight during the first year of antipsychotic treatment.⁴ The effect of metformin on weight in patients with chronic schizophrenia is less well understood. The current study tested the hypothesis that metformin is effective for weight loss in patients with chronic schizophrenia or schizoaffective disorder who are currently overweight and taking one or two Food and Drug Administration (FDA)-approved antipsychotic medications at stable doses.

Methods: In a 16-week, double-blind, randomized trial, 148 outpatients with schizophrenia or schizoaffective disorder with a body mass index (BMI) >27 kg/m² received metformin, titrated to 2000 mg/d, as tolerated, or placebo. All patients also received a behavioral intervention focused on improving diet and exercise habits.

Results: Metformin was associated with significantly greater weight loss than placebo (2.9 kg [95% CI, 1.9-3.9] versus 1.1 kg [95% CI, 0.0-2.1], $p=0.0092$). Metformin also showed a linear group by time interaction on body weight. Among secondary outcomes, an advantage for metformin was also seen for triglycerides. In secondary analyses, metformin appeared to show differential efficacy in patients taking higher (e.g., clozapine, olanzapine, quetiapine) versus lower (e.g., aripiprazole, ziprasidone, haloperidol) metabolic risk antipsychotics on outcomes of weight, total cholesterol and triglycerides. Metformin was generally well tolerated other than expected gastrointestinal disturbances in some patients.

Discussion: Adjunctive metformin for 16 weeks was safe and effective in reducing weight and triglyceride levels among overweight patients with chronic schizophrenia and schizoaffective disorder who were on stable antipsychotic regimens. Metformin may be more effective in patients taking higher metabolic risk antipsychotics, although larger cohorts are needed to better define this effect. Future studies can also address whether longer duration treatment with metformin can further improve weight and other metabolic risk factors for cardiovascular disease in this population.

Source of Funding: National Institute of Mental Health (N01MH90001 P.I.: Lieberman).

Learning Objectives:

- Understand the potential utility of adjunctive metformin for achieving weight loss in overweight patients taking antipsychotic medications
- Understand safety considerations associated with metformin therapy in patients with chronic psychotic disorders

References:

1. Correll CU, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA* 2009;302:1765–73.
2. Lieberman JA, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;353:1209–23.
3. Miller LJ. Management of atypical antipsychotic drug-induced weight gain: focus on metformin. *Pharmacother* 2009;29:725–35.
4. Wu RR, et al. Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. *JAMA* 2008;299:185–93.

Late-Breaking Research Reports

4:00 p.m. – 5:30 p.m.

Metabolomics in the Study of Neuropsychiatric Diseases

Rima Kaddurah Daouk, Ph.D.
Duke University Medical Center

Biomarkers that are specific and sensitive to Alzheimer's disease (AD) would facilitate early diagnosis, disease progression monitoring and drug development. Prior neurochemical and metabolic (e.g., neurotransmitter studies and PET scans) studies have focused on studying a small number of metabolites, and while important findings were derived, no robust biomarkers for AD have been identified. Metabolomics, the global science of biochemistry, provides powerful tools to map perturbations in the metabolic network and enables simultaneous quantification of a large number of metabolites to identify metabolic signatures as biomarkers for disease. In this study, we take a targeted electrochemistry based metabolomics approach where liquid chromatography followed by coulometric array detection enables quantification of over thirty metabolites within key neurotransmitter pathways (dopamine and serotonin) and pathways involved in oxidative stress. Using samples from post-mortem ventricular cerebrospinal fluid (CSF) (15 AD and 15 non-demented subjects with autopsy confirmed diagnoses) and using regression models, correlations, Wilcoxon rank-sum tests and t-tests we identified alterations in tyrosine, tryptophan, purine and tocopherol pathways in patients with AD. These data support further investigation of these profiles in larger samples of clinical AD for utility as biomarkers.

Learning Objectives:

- Examine biochemical changes in norepinephrine and serotonin pathways using metabolomics
- Discuss role of metabolomics as a biomarker in AD diagnosis and drug discovery

Literature References:

Kaddurah-Daouk R, et al. Metabolomics: a global biochemical approach to study of central nervous system diseases. *Neuropsychopharmacol* 2009 Jan.;34(1):173-86.
Kaddurah-Daouk R. Metabolomic profiling of patients with schizophrenia. *PLoS Med* 2006;3(8):e363.

A Multiplexed Immunoassay Profile to Aid Confirmation of Schizophrenia in Clinical Trial Population Enrichment or Depletion

Anthony Barnes, Ph.D.
Rules Based Medicine, Inc.

Rules Based Medicine has developed a serum-based multiplexed immunoassay profile to aid in the confirmation of schizophrenia in patients showing symptoms of serious mental illness. The test measures 51 different analytes using fluorescently labeled immunoassays on a platform (Luminex). The test was validated using 593 patients having either first onset, drug naïve psychosis and diagnosed as schizophrenia or recent onset schizophrenia (up to several years) versus 237 normal matched controls. Mathematical analyses showed the assay to have an optimized sensitivity of 85% and specificity of 84% and an AUROC of 0.89. When the index score assigned to patients was rank ordered and divided into quintiles and the middle quintile removed for retesting at a later time, the specificity for schizophrenia was 95%. Importantly, there was no distinction between the index score and the stage of the illness. This objective detection of a biological signature consistent with schizophrenia suggests that the 51 marker test could be used to confirm the diagnosis in medical situations and delineate the biological consistency of patients and controls included in clinical trials.

Learning Objectives:

- Create awareness of new results in the search for blood based biomarkers for mental illness
- Learn about the methods available to clinical researchers in more accurately identifying clinical trial populations

Literature References:

Mayilyan KR, et al. The complement system in schizophrenia. *Drug News Perspect* 2008;21(4):200-10.
Guest PC, et al. Increased levels of circulating insulin-related peptides in first-onset, antipsychotic naïve schizophrenia patients. *Mol Psychiatry* 2010;15(2):118-9.