ABSTRACT BOOK

ASCP ANNUAL MEETING

LOEWS MIAMI BEACH

JUNE 22-25, 2015

STAGING ILLNESS AND TREATMENT:

FROM PREVENTION TO RECOVERY

ASCP

American Society of Clinical Psychopharmacology

www.ASCPP.org

Sunday, June 21, 2015

12:00 p.m. - 1:15 p.m.
Latin American Psychopharmacology Update: INNOVATIVE TREATMENTS IN PSYCHIATRY

INNOVATIVE TREATMENTS IN PSYCHIATRY

Flavio Kapczinski, The University of Texas Health Science Center at Houston

Overall Abstract In this panel, we will propose innovative treatments in psychiatry and recent literature findings will be summarized. The effective pharmacological treatment of psychiatric diseases and development of new therapeutic entities has been a long-standing challenge. Despite the complexity and heterogeneity of psychiatric disorders, basic and clinical research studies and technological advancements in genomics, biomarkers, and imaging have begun to elucidate the pathophysiology of etiological complexity of psychiatric diseases and to identify efficacious new agents (Tcheremissine et al. 2014). Many psychiatric illnesses are associated with neuronal atrophy, characterized by loss of synaptic connections, increase of inflammatory markers like TNF-α and DAMPS (damage-associate molecular patterns,- cell free (ccf) DNA, heat shock proteins HSP70, HSP90, and HSP60, and cytochrome C), decrease of neurotrophic factors, increase of oxidative stress, mitochondrial dysfunction and apoptosis (Fries et al., 2012; Pfaffenseller et al., 2014). Also, neurocognitive impairment and poor psychosocial functioning has been related to a psychiatric disease. Therefore, trying to discover new therapeutic targets that act in these pathways can help to develop new treatment or improve the treatment of these serious diseases. Furthermore, prompt treatment may be potentially neuroprotective and attenuate the neurostructural and neurocognitive changes that emerge with chronicity in patients with severe psychiatric disorders.

Learning Objectives

- Describe studies to develop new therapeutic targets to treatment of psychiatric disease.
- Learning about new strategies to treat psychiatric disease

SODIUM NITROPRUSSIDE AS A FAST-ACTING ANTIPSYCHOTIC AGENT

Jamie Hallak, University of São Paulo

Individual Abstract Despite decades of study, the etiology and physiopathology of schizophrenia remain unknown. Recent evidence suggests that nitric oxide (NO) may be implicated in schizophrenia. NO is a gas that mediates the release of neurotransmitters, learning, memory, and neurodevelopment. Studies investigating the role of NO in patients with schizophrenia found evidence that points to a disruption in NO-mediated neurotransmission. Therefore, we investigated the effects of sodium nitroprusside, an NO donor, as an add-on treatment for patients with schizophrenia. Twenty adult schizophrenia patients treated with stable doses of antipsychotics were randomly assigned to two groups that received an infusion of either sodium nitroprusside or placebo for four hours. Psychiatric symptoms were assessed at baseline and every hour during the infusion with the Brief Psychiatric Rating Scale (BPRS) and the negative subscale of the Positive and Negative Syndromes Scale (PANNS-n). Additional assessments were made 12 hours after the infusion, daily for seven days, and weekly for four weeks. Cognitive tests (Stroop Color Word Test, N-back, and FAS) were administered at baseline and 12 hours after the end of the infusion. No side effects were reported by the participants. All the clinical and demographic characteristics of the sample including age, education, duration of disease, gender, diagnostic subtype, and type of antipsychotic in use were matched across groups. Symptom ratings were significantly reduced in the group treated with sodium nitroprusside, but not in the placebo group. Cognitive performance was also significantly improved in the nitroprusside group compared to placebo. There were no significant differences between the two groups regarding the physiological parameters analyzed (systolic and diastolic blood pressure, cardiac rhythm, and oxygen saturation). The strategy of treating schizophrenia patients for four hours with 0,5 mcg/kg/min sodium nitroprusside improved psychopathology and cognitive function. Our findings support the hypothesis that the NMDA-NO-GMPc pathway is affected in schizophrenia and that nitric oxide donors such as sodium nitroprusside could thus be a promising approach in the management of the disorder. Although exciting, these results are preliminary and must be replicated by future studies.

Learning Objectives

- Role of NO in schizophrenia
- NO donors as a therapeutical approach in schizophrenia

Literature References

- Hallak JE, Maia-de-Oliveira JP, Abrao J, Evora PR, Zuardi AW, Crippa JA, Belmonte-de-Abreu P, Baker GB, Dursun SM. Rapid improvement of acute schizophrenia symptoms after intravenous sodium nitroprusside: a randomized, double-blind, placebo-controlled trial. JAMA Psychiatry. 2013 Jul;70(7):668-76.
- Maia-de-Oliveira JP, Abrao J, Evora PR, Zuardi AW, Crippa JA, Belmonte-de-Abreu P, Baker GB, Dursun SM, Hallak JE. The effects of sodium nitroprusside treatment on cognitive deficits in schizophrenia: a pilot study. J Clin Psychopharmacol. 2015 Feb;35(1):83-5.

DEEP BRAIN STIMULATION: NEW OPPORTUNITIES IN NEUROPSYCHIATRY

Roger Walz, AFSC

Individual Abstract Deep brain stimulation (DBS) consists of a neural-network modulation of dysfunctional brain circuits by electric stimulation through steretatically implanted electrodes. The technique has been successfully applied to treat movement disorders. Several reports raise the possible use of DBS to treat pharmacologically refractory neuropsychiatric diseases including: depression, obsessive-compulsive disorder, Gilles de la Tourrete, addictive behavior, obesity, anorexia nervosa, Alzheimer´s, epilepsies and aggressive behavior. The mechanisms of DBS action remain unknown, and understanding the effects of electrical stimulation on brain functions is a fascinating opportunity for basic and clinical research. DBS is an expanding area that offers an endless array for multidisciplinary research involving physicians, engineers and basic neuroscientists. We will discuss some of the promising and challenges aspects related to the clinical applications of DBS in neuropsychiatry.

Learning Objectives

- To present some possible applications of DBS in neuropsychiatry
- To discuss some challenges related to DBS clinical use in neuropsychiatric diseases

Literature References

- Williams NR and Okun MS. Deep brain stimulation (DBS) at the interface of neurology and psychiatry. J Clin Invest 2013;123: 4546–4556.
- Krack P, Hariz MI, Baunez C, Guridi J, and Obeso JA. Deep brain stimulation: from neurology to psychiatry? TINS 2010; 33: 474-484.

1:15 p.m. - 2:30 p.m.
Latin American Psychopharmacology Update: NEW PHARMACOLOGICAL TARGETS: FROM PRE-CLINICAL MODELS TO PATIENT CARE

NEW PHARMACOLOGICAL TARGETS: FROM PRE-CLINICAL MODELS TO PATIENT CARE

Marco Romano-Silva, Universidade Federal de Minas Gerais

Overall Abstract The number of non-responding patients to current treatments is still unacceptably high, reaching 30% or more in some disorders. Thus, the search for new targets is essential and urgent. Identification of new targets for pharmacological therapy of psychiatric disorders will be presented in this session, with focus on major depression, late life depression and schizophrenia.

Learning Objectives

- To discuss new strategies for the treatment of major depressive disorder and late life depression.
- To discuss the efficacy of memantine as an adjunctive treatment in schizophrenia.

NEUROCHEMICAL MECHANISMS UNDERLYING KETAMINE ANTIDEPRESSANT EFFECT

João de Quevedo, The University of Texas Health Science Center at Houston

Individual Abstract Major depressive disorder (MDD) affects about 121 million of global population and poses a significant burden to the healthcare sector. Nevertheless, around 50-60% of patients with MDD respond adequately to existing treatments. In addition, the neurobiology of MDD as well as drug action mechanism is not yet fully elucidated. Recently, studies have demonstrated the key role of the glutamatergic system in both pathophysiology and treatment of MDD. Ketamine, an N-methyl-D-asparte (NMDA) receptor antagonist has been proposed as potential revolutionary rapid antidepressant agents for treatment-resistant mood disorders. Preclinical studies have been shown that ketamine stimulate the mammalian target of rapamycin (mTOR), which is involved in neuroplasticity, cell survival and proliferation, including brain-derived neurotrophic factor (BDNF) and MAPK signaling. In addition, ketamine decreases oxidative stress and inflammation in rodents subjected to animal models of depression. Thus, current and future research studies are using ketamine as a promising tool to evaluate the glutamatergic neurotransmitter system to learn more about the pathophysiology of depression and develop more specific rapid-acting antidepressant treatments. Thus, this panel will summarize recent findings from literature.

Learning Objectives

- New strategies to major depressive disorder treatment.
- Preclinical and clinical studies showing evidences that glutamatergic system is involved with depression.

Literature References

- Lally N, Nugent AC, Luckenbaugh DA, Niciu MJ, Roiser JP, Zarate CA Jr: Neural correlates of change in major depressive disorder anhedonia following open-label ketamine. J Psychopharmacol 2015, in press.
- Réus GZ, Nacif MP, Abelaira HM, Tomaz DB, dos Santos MA, Carlessi AS, da Luz JR, Gonçalves RC, Vuolo F, Dal-Pizzol F, Carvalho AF, Quevedo J: Ketamine ameliorates depressive-like behaviors and immune alterations in adult rats following maternal deprivation. Neurosci Lett 2015;584:83-7.

BIOLOGICAL MARKERS IN MOOD DISORDERS IN ELDERLY PATIENTS

Breno Satler Diniz, Department of Mental Health, Faculty of Medicine, Federal University of Minas Gerais

Individual Abstract Late-life depression (LLD) is a common disorder in the elderly is linked to worse functioning and poorer treatment outcomes, significantly increase the risk of dementia and mortality. Its pathophysiologic mechanisms is largely unknown, but probably involve abnormalities in multiple biological cascades. In a recent study, including 80 subjects with LLD and 31 healthy controls, we carried out a comprehensive analysis of biomarkers related to LLD. We used a data-driven comprehensive proteomic analysis (multiplex immunoassay including 242 proteins), along with measures of structural brain abnormalities (gray matter atrophy and white matter hyperintensities volume via magnetic resonance imaging). We found that a biosignature including the abnormal expression of more than 40 proteins in plasma and structural brain changes are significantly associated with LLD. The analysis of the molecular and biological pathways related to this biosignature revealed the association with greater cerebrovascular disease along with reduced neurotrophic support, abnormalities in immune–inflammatory control, cell survival, intracellular signaling, protein and lipid homeostasis, clotting processes, nutrient sensing and mitochondrial dysfunction. These results demonstrated that subjects with LLD bear multiple neurobiological abnormalities that can render them more vulnerable to accelerated brain aging and progressive brain changes. Our findings shed light on possible mediators of the elevated risk for progression to dementia, in particular to Alzheimer's disease and vascular dementia, among these subjects. Finally, we provide novel targets for prevention and treatment of LLD, as well as, for its downstream negative outcomes, including the development of dementia and related disorders.

Learning Objectives

- The pathophysiology of late-life depression in complex and involves abnormalities in multiple biological cascades.
- Data-driven proteomic analysis associated with structural neuroimaging can reveal novel biological pathways related to LLD.

Literature References

- Diniz BS, Teixeira AL, Machado-Vieira R, Talib LL, Radanovic M, Gattaz WF, Forlenza OV. Reduced cerebrospinal fluid levels of brain-derived neurotrophic factor is associated with cognitive impairment in late-life major depression. J Gerontol B Psychol Sci Soc Sci. 2014 Nov;69(6):845-51. doi: 10.1093/geronb/gbu096.

- Diniz BS, Sibille E, Ding Y, Tseng G, Aizenstein HJ, Lotrich F, Becker JT, Lopez OL, Lotze MT, Klunk WE, Reynolds CF, Butters MA. Plasma biosignature and brain pathology related to persistent cognitive impairment in late-life depression. Mol Psychiatry. 2014 Aug 5. doi: 10.1038/mp.2014.76. [Epub ahead of print]

MEMANTINE AS AN ADJUNCTIVE TREATMENT IN SCHIZOPHRENIA

Clarissa Gama, UFRGS, HCPA, Porto Alegre, Brazil

Individual Abstract Memantine, a drug approved by the FDA for the treatment of moderate to severe Alzheimer's disease cognitive impairment, acts as weak non-selective N-methyl-d-aspartate receptor (NMDA) receptor antagonist and has been used off-label for various psychiatric disorders. An investigator-initiated clinical trial from our group was published showing cognitive improvement with memantine in patients with schizophrenia. This study was the first randomized placebo-controlled clinical trial with memantine adjunctive to clozapine for the treatment-refractory schizophrenia. A strong and significant effect size favoring memantine was seen on Mini-Mental State Exam, total Brief Psychiatric Rating Scale and its positive and negative subscales.

Learning Objectives

- To discuss the efficacy of memantine as an adjunctive treatment in schizophrenia.
- To discuss the role of memantine in direct modulation of glutamate, as partial NMDA agonist receptor, and its role on cognition, learning and new memories recall.

Literature References

- Zdanys K, Tampi RR. A systematic review of off-label uses of memantine for psychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(6):1362-74.
- de Lucena D, Fernandes BS, Berk M, Dodd S, Medeiros DW, Pedrini M, Kunz M, Gomes FA, Giglio LF, Lobato MI, Belmonte-de-Abreu PS, Gama CS. Improvement of negative and positive symptoms in treatment-refractory schizophrenia: a double-blind, randomized, placebo-controlled trial with memantine as add-on therapy to clozapine. J Clin Psychiatry. 2009 Oct;70(10):1416-23.

2:45 p.m. - 4:00 p.m.

Latin American Psychopharmacology Update: DEVELOPING NEW TARGETS FOR PHARMACOLOGICAL INTERVENTIONS

DEVELOPING NEW TARGETS FOR PHARMACOLOGICAL INTERVENTIONS

Jair Soares, University of Texas School of Medicine at Houston

Overall Abstract In this panel we will review recent literature findings and discuss possible new targets for pharmacological interventions in psychiatric disorders. Developing new pharmacotherapies for these disorders is a complex challenge, but considerable progress has been made in the past decade surrounding the underlying mechanisms and treatment. Basic and clinical research studies, propelled by technological advancements in genomics, biomarkers and brain imaging, have begun to elucidate the mechanisms involved and unravel their pathophysiology. The literature shows strong evidence of alterations in peripheral biomarkers like inflammatory markers, neurotrophic factors, oxidative stress, mitochondrial dysfunction and apoptosis in psychiatric patients. In addition, brain abnormalities have been widely reported in neuroimaging studies. These studies suggest incremental volume loss in brain networks that are affected in psychiatric disorders. Furthermore, neurocognitive impairment and poor psychosocial functioning have been documented and account for worse response to pharmacological and psychosocial interventions. Despite the complexity and heterogeneity of psychiatric disorders and the enormous difficulty in developing novel treatments, there is considerable hope brought up by new leads on the molecular mechanisms and novel therapeutic possibilities. As new targets are discovered and innovative pharmacological interventions are developed, we anticipate considerable impact on the prevention and early treatment of these conditions.

Learning Objectives

- Discuss new pharmacological interventions for psychiatric disorder.
- Describe development of new therapeutic targets to treatment of psychiatry disease.

NEURO-INFLAMMATION IN PSYCHIATRIC DISORDERS: PROMISES AND EVIDENCE

Antonio Teixeira, Universidade Federal de Minas Gerais

Individual Abstract Inflammation is traditionally regarded as a body response against different insults, including microorganisms and trauma. A more recent view of the inflammatory process proposes its role as a homeostatic system that works in parallel with other physiological systems, mainly nervous and endocrine systems. This conceptual change has both theoretical and clinical implications. In this scenario, several studies have described inflammatory and/or immune dysfunction in psychiatric disorders. There are at least five lines of evidence on immune dysfunction in bipolar disorder: (i) increased frequency of autoimmune diseases; (ii) distinct immune cell profile; (iii) altered release of cytokines by stimulated mononuclear cells; (iv) high levels of circulating immune markers, and (v) inflammatory changes in the central nervous system (Barbosa et al., 2014b). It is still uncertain whether peripheral immune parameters (i.e. peripheral signature) reflect ongoing pathophysiological processes in the central nervous system. Despite this, these parameters have been proposed as prognostic biomarkers of mood disorders with promising results (Barbosa et al., 2014a). Immune mechanisms are also potential targets for the development of pharmacological strategies to reduce the burden associated with psychiatric disorders. Only a few trials have addressed this issue, and there is a great avenue of opportunity for clinical research

Learning Objectives

- Describe the evidence of immune and/or inflammatory dysfunction in psychiatric disorders, focusing on mood disorders.
- Discuss the potential clinical and therapeutic implications of this evidence.

Literature References

- Barbosa IG, Bauer ME, Machado-Vieira R, Teixeira AL. Cytokines in bipolar disorder: paving the way for neuroprogression. Neural Plast. 2014;2014:360481. (a)
- Barbosa IG, Machado-Vieira R, Soares JC, Teixeira AL. The immunology of bipolar disorder. Neuroimmunomodulation. 2014;21(2-3):117-22. (b)

GENETIC DETERMINANTS OF DRUG RESPONSE

Rodrigo Nicolato, UFMG

Individual Abstract Pharmacogenetics can be defined as the study of the influence of specific genes in response variability and drug tolerability. The pharmacogenetic studies are generally based in the search for candidates or unique genes: researchers elect a gene and its polymorphisms as a candidate for association with a trait or disease. Then recruit this population with characteristic or disease, and the prevalence of polymorphisms research in an attempt to detect a statistically significant correlation between genetic variation and the characteristic under study. Depression and schizophrenia are frequent psychiatric disorders, chronic, recurrent and promoting breakdown and extensive social cost. Psychopharmacology presents an increasing number of effective drugs and their evolution occurs to increase the effectiveness of the treatment of refractory patients, as well as reduce the common side effects associated with traditional drugs. Considering that pharmacotherapy is an effective treatment, 30-50% of patients do not respond to treatment and another substantial portion presents significant side effects. Despite the growing variety of drugs available for treatment of psychopathology, are still needed many improvements in the available drugs or even the creation of better drugs.

Learning Objectives

- Main aspects related to pharmacogenetic response to psychotropic drugs;
- The study of genetic polymorphisms in the field of psychopharmacology.

Literature References

- Malhotra AK, Murphy GM Jr, Kennedy JL.Pharmacogenetics of psychotropic drug response.Am J Psychiatry. 2004 May;161(5):780-96.
- Hamilton SP.The promise of psychiatric pharmacogenomics.Biol Psychiatry. 2015 Jan 1;77(1):29-35.

NEUROPROGRESSION: FROM CONCEPTUAL DEVELOPMENT TO PHARMACOLOGICAL INTERVENTIONS

Flavio Kapczinski, The University of Texas Health Science Center at Houston

Individual Abstract In this panel, neuroprogression in Bipolar Disorder (BD) will be summarized. BD is a significant burden to the healthcare sector that affects 1-3% of the global population. Among the major hypotheses for the neurobiology of BD, neuroprogression is gaining significant attention. The term "neuroprogression" has been proposed to describe the pathological rewiring of the brain that takes place when clinical and cognitive deterioration occurs in the context of the progression of BD. Neuroprogression is characterized by stage-related progressive changes in the frequency of episodes, inter-episodic intervals, response to medications, comorbidity risks, altered levels of systemic inflammatory markers, oxidative stress markers, apoptosis and mitochondrial dysfunction in addition to structural changes in specific brain regions (Fries et al., 2012; Pfaffenseller et al., 2014, Berk et al., 2011). Also, neurocognitive studies reported that BD patients at late stages were significantly more impaired than those at early stage of this illness in distinct domains of functioning. These inherently modifiable factors have known neuroadaptive and neurodegenerative implications, and consequently, may provide useful biomarker targets. Identification of these factors early in the course of the disease will accordingly allow for the introduction of early interventions and may improve the individual's capacity for psychological resilience through maintenance of synaptic integrity and cellular resilience

Learning Objectives

- Describe the concept for neuroprogression in Bipolar Disorder.
- Interventions that can prevent or decrease the neuroprogression in Bipolar Disorder.

Literature References

- Berk M, Brnabic A, Dodd S, et al. Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. Bipolar Disord 2011; 13: 87–98.
- Fries GR, Pfaffenseller B, Stertz L, Paz AV, Dargél AA, Kunz M, Kapczinski F. Staging and neuroprogression in bipolar disorder. Curr Psychiatry Rep 2012; 14: 667-75.
- Pfaffenseller B, Wollenhaupt-Aguiar B, Fries GR, Colpo GD, Burque RK, Bristot G, Ferrari P, Ceresér KM, Rosa AR, Klamt F, Kapczinski F. Impaired endoplasmic reticulum stress 136 response in bipolar disorder: cellular evidence of illness progression. Int J Neuropsychopharmacol. 2014; 17:1453-63.

Monday, June 22, 2015

9:00 a.m. - 10:30 a.m.

Panel Session

FROM AGITATION TO AGGRESSION: PHARMACOTHERAPY AND OTHER INTERVENTIONS - SEQUENCES, COMBINATIONS, AND TARGETS

Leslie Citrome, New York Medical College

Overall Abstract Violent behavior associated with mental disorders is a common reason for admission to a psychiatric inpatient unit. Once hospitalized, patients may continue to be intermittently agitated and have persistent aggressive behaviors, preventing their discharge back into the community. Managing agitation quickly with effective pharmacological agents and non-pharmacological interventions can avoid further escalation to aggression and violence. In the acute setting this usually involves the parenteral use of antipsychotics, with or without benzodiazepines. Within the past decade, short-acting intramuscular formulations of second-generation antipsychotics have become available and provide a means to induce calm with a substantially lower risk of acute dystonia or akathisia compared with haloperidol. New alternative formulations that avoid injections include inhalation and sublingual administration. Longer-term management of persistent aggressive behavior by reducing the frequency and intensity of future episodes of agitation is more complex. In contrast to agitation associated with schizophrenia or bipolar mania, no agents have yet been approved by regulatory agencies for the treatment of persistent aggressive behavior.

The strongest evidence supports the use of clozapine as an anti-hostility agent, followed by olanzapine. Adjunctive strategies with anticonvulsants and beta-adrenergic agents may also be worthwhile considering.

Learning Objectives

- To understand the different interventions available for the management of acute agitation and aggressive behavior.
- To understand the different interventions intended to reduce the intensity and frequency of future episodes of agitation and aggression.

UNDERSTANDING THE PSYCHIATRIC PAIN AND DISTRESS ASSOCIATED WITH AGITATION - EVALUATION AND ASSESSMENT OF THE AGITATED PATIENT USING THE PROJECT BETA GUIDELINES

Scott Zeller, Alameda Health System

Individual Abstract Agitation is an acute behavioral emergency that is encountered millions of times annually in USA emergency departments and psychiatric units. Agitation may be caused by a number of different medical and psychiatric conditions, and a prompt triage and diagnostic assessment is essential to safely proceed with treatment. Misdiagnosis can have severe and even life-threatening consequences. This presentation will describe the diagnostic features of the full spectrum of agitation, and discuss consensus evidence-based best practices in rapid triage and evaluation of agitation states, including assessment algorithms.

Verbal De-Escalation and other calming techniques are integral to interventions with agitated individuals, and may reduce the risk of progression to aggression and violence. This presentation will include discussion of the de-escalation guidelines reported in the Project BETA studies (Best Practices in the Evaluation and Treatment of Agitation). Implementation of the BETA guidelines have led to dramatic decreases in the use of physical restraints and forced involuntary medications in numerous hospitals worldwide, while concurrently also resulting in reductions in assaults and staff injuries. Effective use of De-Escalation techniques combined with appropriate and timely medication administration has also been shown to improve throughput times in emergency departments, and is correlated with elevated patient satisfaction scores.

Learning Objectives

- Identify the best practices in triage and medical evaluation of an agitated patient.
- Demonstrate techniques of verbal de-escalation which can help to calm an agitated individual.

Literature References

- Holloman GH Jr, Zeller SL. Overview of Project BETA: Best practices in Evaluation and Treatment of Agitation. West J Emerg Med. 2012 Feb;13(1):1-2.
- Nordstrom K, Zun LS, Wilson MP, et al. Medical evaluation and triage of the agitated patient: consensus statement of the American Association for Emergency Psychiatry Project BETA Medical Evaluation Workgroup. West J Emerg Med. 2011;13:3–10.
- Richmond JS, Berlin JS, Fishkind AB, et al. Verbal de-escalation of the agitated patient: consensus statement of the American Association for Emergency Psychiatry Project BETA De-escalation Workgroup. West J Emerg Med. 2011;13:17–26.

ASSUAGING AGITATION: INGEST, INJECT OR INHALE?

Michael Allen, University of Colorado School of Medicine

Individual Abstract Speed of response is critical in the setting of agitation where timely intervention may prevent escalation to violence. At one time, this was the only consideration in the choice treatments for agitation and there was a general sense in the field that intramuscular drugs were faster and hence better than oral. In fact, there is significant variation in IM absorption and onset of action with little advantage for injectables over oral in many cases. IM droperidol set the benchmark for speed with antipsychotics at one time but with controversial concerns about QTc prolongation. Somnolence was also considered desirable at one time but over-sedation is now generally viewed as adverse. More recently, there have been a number of new drugs and formulations and the data and choices have become more complex. Some second generation antipsychotics have been formulated to dissolve orally. Only asenapine is absorbed in the oropharynx and it has separated from placebo in agitated patients at 15 min. Otherwise, oral solutions are still swallowed and absorbed in the gut though they avoid the problem of "cheeking". Several second generation antipsychotics are now available as rapid acting injections including intramuscular zirpasidone, olanzapine, and aripiprazole. Some are faster than IM haloperidol, some are not and all are similar to haloperidol at 2 hours, as evidenced by the number needed to treat for treatment response vs. placebo. Now inhalation of loxapine offers the prospect of delivering drug directly to the systemic circulation, avoiding the vagaries of enteral absorption and first pass metabolism or peripheral venous access through different capillary beds. This comes with faster onset but also new pulmonary adverse effects. Both orally dissolving and inhalation routes may preserve patient autonomy to a greater extent but require some degree of cooperation. The field must now be viewed then in terms of degrees of agitation and cooperation as well as speed, endpoints and adverse effects. This presentation will discuss the measurement of agitation, the spectrum of presentations, selection of patients for different treatments, the desired endpoint and salient side effects.

Learning Objectives As a result of this presentation, attendees will be able to:

- Describe different methods for delivering drugs including orally dissolving, rapid IM and inhalation methods.
- Quantify the severity of agitation on a spectrum.
- Describe factors to consider in selecting treatments including the degree of autonomy possible, speed of response and salient side effects.
- Identify patient groups appropriate for different treatments.

Literature References

- Nordstrom K and Allen MH: Alternative Delivery Systems for Agents to Treat Acute Agitation: Progress to Date. Drugs 2013; 73:1783-1792
- Allen MH, Feifel DA, Lesem MD, Zimbroff DL, Ross R, Spyker DA and Cassella JV. Efficacy and Safety of Loxapine for Inhalation in the Treatment of Acute Agitation in Patients with Schizophrenia: A Randomized, Double-blind, Placebo-controlled Trial. J Clin Psychiatry. 2011;72(10):1313–1321.

FROM PHARMACOEPIDEMIOLOGICAL STUDIES AND POST HOC ANALYSES TO RANDOMIZED CONTROLLED TRIALS: PREVENTING AGGRESSIVE EPISODES

Leslie Citrome, New York Medical College

Individual Abstract Preventative treatment aims to decrease the frequency and intensity of future acute episodes of agitated, aggressive, and violent behavior, and although effective therapeutic options do exist, they are far from being ‘‘one size fits all,’’ and are highly dependent on the root causes of the dangerous behaviors. Examples of potential contributors to violent behavior include psychosis, psychopathy, impulsivity, co-occurring substance or alcohol use, cognitive impairments, or underlying somatic conditions. Adverse drug reactions such as akathisia can be subtle and are often missed. Thus effective treatment approaches can vary considerably depending on the specific characteristics of the individual being treated. With few exceptions, most of the clinically relevant research on the longer-term management of violence has been conducted in psychotic individuals with schizophrenia. In general, receiving medications can reduce the risk of violent crime, as evidenced in Sweden where compared with periods when participants were not on medication, violent crime fell by 45% in patients receiving antipsychotics. The type of formulation of the antipsychotic may also play a role in the prevention of recidivism among persons with a history of involvement with the criminal justice system, where a randomized controlled trial of a long-acting injectable antipsychotic was superior to oral antipsychotic treatment in delaying time to treatment failure, including events of arrest and incarceration. Specific anti-hostility and anti-aggressive effects of clozapine have been demonstrated in prospective double-blind randomized controlled trials. However, the the evidence for these specific effects for the other second-generation antipsychotics have largely come from post hoc analyses of studies originally conducted primarily for other purposes, such as registration trials and effectiveness studies. Olanzapine has demonstrated advantages in terms of a specific antihostility effect over the other antipsychotics tested in Phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) as well as in the European First-Episode Schizophrenia Trial (EUFEST). Augmentation strategies where non-antipsychotic medications are added to an antipsychotic in order to reduce the frequency of aggressive or violent behavior are also used, but the evidence base for this is mixed.

Learning Objectives

- Recognize that hostile and aggressive behavior is etiologically heterogeneous.
- Review the supporting evidence for the the specific anti-hostility and anti-aggressive effects of antipsychotics and other pharmacological agents.

Literature References

- Citrome L, Volavka J. The psychopharmacology of violence: making sensible decisions. CNS Spectr. 2014 Oct;19(5):411-8.
- Volavka J, Citrome L. Heterogeneity of violence in schizophrenia and implications for long-term treatment. Int J Clin Pract. 2008 Aug;62(8):1237-45.

CLINICAL RESEARCH SUBJECT REGISTRIES: PAST EXPERIENCE AND FUTURE DIRECTIONS

Kerri Weingard, Verified Clinical Trials

Overall Abstract It has long been recognized that duplicate enrollment in clinical trials that investigate subjective disease states has presented many hurdles to conducting a successful trial. In particular multiple simultaneous enrollment within CNS clinical trials possess unique inherent obstacles to research sites, pharmaceutical companies and CROs. The research subject’s failure to admit to simultaneous participation in more than one clinical trial and jumping from one trial to another without allowing sufficient time to lapse between treatments compromises not only compromises the health of the subjects, but negatively impacts the data quality. This leads to a perceived lack of efficacy of the investigational compound with increased placebo as well as potential increased adverse events.. The issue of dual enrollment provoked three separate companies to create an ID metric research subject database to prevent this avoidable protocol violation. Verified Clinical Trials (VCT) , CTS database and DupCheck have each created ID-metric research subject registries to improve the quality of the research subjects that are screened and ultimately randomized in to a clinical trial. This panel discussion will involve a thorough discussion of each of the currently available ID-metric research subject registries. The panel will discuss the data, metrics surrounding both early and late phase attempted duplicate enrollment as well as additional technologies for protocol violation prevention. The panel will explore the challenges and successes that surround the registries. Additionally progress towards integration of said systems versus redundancy. The topic can the ID metrics systems work together to create a stronger network of protection for the CNS subjects and trials will be tackled. Lastly, what is the future direction for research subject databases in the United States and globally will allow the open discussion to continue.

Learning Objectives

- How research subject databases work to improve subject safety and improve data quality.
- How by working together the three major ID metric research subject databases can make a significant impact in reducing protocol violations and saving the Pharmaceutical Sponsors, CROs and Research sites time and monies.

REDUNDANCY OR INTEGRATION: THE FUTURE OF SUBJECT REGISTRIES?

Thomas Shiovitz, California Neuroscience Research

Individual Abstract Purpose: This talk will examine how integrating existing subject registry systems might improve efficiency and success of CNS clinical trials. These ideas - which would bring together vendor competitors to benefit CNS trial execution - have not been explored in other venues.

Content, Methodology, Results: While clinical trial registries have attempted to reduce dual subject enrollment for over seven years, several national registries have become more extensively utilized in the last 3-4 years, especially in CNS and Phase 1 studies.

Recently, pharmaceutical sponsors and investigators have been asking if there is a way that the major registries can “talk to each other” to reduce redundancy and increase the chances of picking up duplicate subject.

If this were to happen, how might this occur? There are several options:

1. Each registry remains separate. Sponsors try them individually or two at a time and choose the one that provides the best service for future protocols. Within three years there is a clear preference for the services of one vendor. The other vendors fold their services into the lead registry.
2. Government (or a consortium of pharma) develop and mandate use of a centralized registry for all subjects in all clinical trials (as in ClinicalTrials.Gov), which, after a period of several years, replaces or integrates with the private registries.
3. A single website could be developed that allows duplicates to be checked at all three registries from a single access point for a single fee (as in Equifax, Transunion and Experian).

4. The registries learn to "talk" to each other. This integration would take significant resources but would allow access to all the databases when any of the databases were utilized. Integration between all three systems is technically possible using Application Programming Interfaces (APIs). APIs help disparate software systems to communicate with each other through a secure SSL tunnel. It would require extensive collaboration between the technical teams of all three systems to design the specifications for a standard API and many months to design, test and get the API production ready. In this manner each system could send and receive information from each other about subject enrollments using the call and send parameters defined in the joint specifications.

Conclusion: For the time being, sponsors should continue to use single or redundant registry systems to reduce duplicate enrollment. They are easy enough to use and add only a small amount to the complexity of studies. However, the desire to increase the efficiency and sensitivity of competing subject registries is likely to lead to significant consolidation or integration in the near future.

Learning Objectives

- Attendees will understand the extent of the duplicate/ professional subject problem and the role of subject registries to detect and eliminate them.
- Attendees will be able to identify at least two ways that available subject registries may work together to increase future efficiency in catching duplicate subjects.

Literature References

- Kass NE, Myers R, Fuchs EJ, Carson KA & Flexner C, Balancing Justice and Autonomy in Clinical Research with Healthy Volunteers. Clin Pharmacol. Therap. 2007; 82:219-227.
- Shiovitz TM, Zarrow ME, Schonberg SH, Seikh LM, Catch Me If You Can: How a Subject Registry Combines Voluntary, Investigator-based Use at Prescreen and Sponsor-mandated Use at Screen to Reduce Duplicate Enrollment. Poster. American College of Neuropsychopharmacology. Dec. 2014; Phoenix, AZ.

THE DUPLICATE AND PROFESSIONAL SUBJECT PROBLEM AND PROPOSED SOLUTIONS

Jonathan Rabinowitz, Bar-Ilan University

Individual Abstract The randomized controlled clinical trial is designed to implement an experimental design, the details of which are presented in the clinical trial protocol. Inclusion and exclusion criteria detailed in the protocol insure that only the appropriate population of patients is enrolled in the clinical trial. In the lab setting, strict procedures are possible, such as selecting specially bred animals and controlling all stimuli. That is not possible in randomized controlled human trials. During the screening process for the clinical trial, the study's inclusion and exclusion criteria are reviewed for each potential participant. Many exclusion criteria depend on laboratory results or clinical findings for confirmation of a patient's eligibility in the clinical trial, for example, pregnancy or cardiac irregularity. An almost universal exclusion criterion is the concomitant use of another investigational drug. At screening, patients are typically asked: "Are you, or have you been, within the last 30 days (sometimes as long as 1 year) on an investigational drug." A negative answer to the question, together with meeting all other criteria allows the patient to enter the study. Like other exclusion criteria, there is clearly a need for a test. France, UK and some parts of Switzerland have implemented mandatory registration of phase I subjects in shared database to prevent concomitant enrollment. There has been a recent call to do the same in the US. Recently efforts have been made to implement registries covering all clinical trials, not just Phase I studies. Because of mobility of populations a single jurisdiction or even a national registry in many areas is likely to be incomplete. Challenges in implementing such systems have included protecting patients and sponsors information, the need for cross-sponsor collaboration, the need to cover all indications, privacy laws, minimizing burden to research sites and obtaining regulatory review.

Learning Objectives

- Participants will understand the scientific, medical and legal impediments posed by duplicate enrollment.
- Participants will learn about the challenges to implementing systems for preventing concomitant enrollment.

Literature References

- Rabinowitz J: Novel Methods Leading to New Medications in Depression and Schizophrenia (NEWMEDS) Consortium. In Sharing clinical research data: Workshop summary. Edited by National Research Council. Washington, DC, The National Academies Press; 2013.
- Abadie R: The professional guinea pig: Big Pharma and the risky world of human subjects. Durham N.C., Duke University Press; 2010.

VERIFIED CLINICAL TRIALS, DUPCHECK AND CTSDATABASE: CURRENTLY AVAILABLE REGISTRY SOLUTIONS TO PREVENT DUPLICATE ENROLLMENT

Mitchell Efros, Verified Clincial Trials

Individual Abstract Purpose: The success and validity of a clinical research trial is largely dependent upon selecting the proper research subject to participate in a clinical trial.

This is especially relevant in clinical trials that rely upon subjective data collection such as psychiatric and CNS disorders. Unfortunately some participants are not entirely forthcoming and have ulterior motives for joining a particular trial. This talk will review the registries that are currently available to select a better quality research subject and prevent duplicate enrollment and protocol violations related to current and prior clinical trial enrollment status.

Content, Methodology, Results: This section will review the three current registries that exist highlighting the capabilities of each system to improve research subject safety and data quality by preventing duplicate enrollment and protocol deviations in a HIPAA compliant manner.

1. The data points collected by each registry will be compared.
2. The systems will be compared with regard to information generated and provided to the research site so that a decision can be reached whether the potential participant is allowed to proceed with the current trial.

Learning Objectives

- Become aware of the various tools and registries available to prevent duplicate enrolment in clinical trials and improve research subject safety and data quality.
- Understand the capabilities, similarities and differences of the established registries.

Literature References

- Healthy Volunteer Registries and Ethical Research Principles. E A Kupetsky-Rincon and W K Kraft. Clinical Pharmacology and Therapeutics 2012
- Stanton D. How Prevalent Is Dual Enrollment In Clinical Trials? Opinion Split Outsourcing-Pharma.com. 2014. *Gary Zammit, Clinilabs, Inc.*

MANAGING COMPLICATED ATTENTION DEFICIT HYPERACTIVITY DISORDER WITH COMORBID DEPRESSIVE AND ANXIETY DISORDERS

Martin Katzman, START Clinic for Mood and Anxiety Disorders

Overall Abstract Prevalence of Attention Deficit Hyperactivity Disorder (ADHD) has been on the rise globally and results in significant negative consequences throughout the lifespan. Early and accurate detection of ADHD is often compromised due to comorbid psychiatric disorders, as there is often significant overlap of symptomatology among these comorbid disorders. This ultimately results in further individual psychosocial impairments, as well as increased personal challenges and societal economic burden. Clinicians are often challenged by the heterogeneity of presenting symptoms, which translates into delays in optimal and appropriate treatment. It is therefore crucial to develop standard diagnostic methods that accurately detect ADHD in the context of comorbidity.

This panel will address the difficulties that exist for clinicians in arriving at a timely and accurate diagnosis of ADHD in patients with co-existing depressive and/or anxiety disorders. The use of a multimodal approach for accurate detection will be reviewed in order to improve patient outcome and overall quality of life. Furthermore, a review of the neurobiological factors will focus on cognitive alterations and dysfunction in the presence of ADHD and comorbid disorders.

The epidemiology and risk factors of these comorbid disorders, as well as the diagnostic challenges that present to clinicians will be comprehensively reviewed.

We will continue this discussion through the examination of the neurobiological correlates associated with cognitive functioning in ADHD and comorbid depressive and/or anxiety disorders.

During this panel, we will review the current scientific literature in order to better understand methods of early and accurate detection. Throughout the panel, case studies will be utilized to further clarify current diagnostic techniques, as well as when to introduce appropriate and efficacious treatment strategies. This panel is designed for clinicians and practitioners interested in improving their knowledge and expertise in the management of complicated cases of ADHD that are comorbid with depressive and/or anxiety disorders.

Learning Objectives

- Identify diagnostic challenges and risk factors that exist in the management of patients with ADHD and comorbid depressive and/or anxiety disorders.
- Understand how the neurobiological correlates and subtle structural alterations associated with cognitive dysfunction exhibited in patients with ADHD and comorbidities.

PHARMACOTHERAPEUTIC TREATMENT STRATEGIES FOR PATIENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND COMORBID DEPRESSIVE AND ANXIETY DISORDERS

Larry Klassen, Eden Mental Health Centre

Individual Abstract Treatment of Attention Deficit Hyperactivity Disorder (ADHD) is often compromised by comorbid psychiatric disorders, specifically depressive and anxiety disorders. It is therefore essential to accurately diagnosis each presenting disorder in order to determine the prioritization of treatment. Effective pharmacological treatment therefore depends upon accurate detection, differentiation, and prioritization of resulting dysfunction of each comorbid disorder. A systematic approach through the use of scientific evidence, will overview methods in accurate detection in order to appropriately manage individuals through pharmacotherapeutic treatment. All synergistic and adverse effects of discussed strategies will be reviewed, including their impact of cognition, mood, and stability. Furthermore, case studies will be utilized throughout in order to better understand appropriate and effective pharmacotherapeutic treatment strategies.

Learning Objectives

- Understand how to accurately detect and prioritize treatment for each presenting disorder.
- Develop a multimodal approach in pharmacotherapeutic treatment strategies in order to achieve optimal outcome.

Literature References

- Gammon GD, Brown TE: Fluoxetine and methylphenidate in combination for treatment of attention deficit disorder and comorbid depressive disorder. Journal of Child and Adolescent Psychopharmacology 2009; 3(1):1-10.
- Kratochvil CJ, Newcorn JH, Arnold LE, Duesenberg D, Emslie GJ, Quintana H, et al.: Atomoxetine alone or combined with fluoxetine for treating ADHD with comorbid depressive or anxiety symptoms. Journal of the American Academy of Child & Adolescent Psychiatry 2005: 44(9):915-924.

CHALLENGES IN THE DETECTION AND DIAGNOSIS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN THE PRESENCE OF COMORBID DEPRESSIVE AND ANXIETY DISORDERS

Irvin Epstein, START Clinic for Mood and Anxiety Disorders

Individual Abstract Recent research has identified an increased prevalence in Attention Deficit Hyperactivity Disorder (ADHD) in adulthood as well as the rate of comorbid psychiatric conditions including depressive and anxiety disorders. These comorbid disorders often present with a myriad of heterogeneous and overlapping symptoms and often result in chronic impairments in multiple domains of an individual's psychosocial functioning. The presence of these comorbidities may also lead to challenges for arriving at a timely and accurate diagnosis, which in turn impacts negatively on treatment outcome and on one's psychological wellbeing. This review will focus on the current evidence regarding the epidemiology and biological factors associated with ADHD in the presence of comorbid depressive and anxiety disorders. Emphasis will be given to the associated cognitive alterations and dysfunction attributed to each comorbid disorder and implications in an individual's functional outcome. A number of case studies will be utilized throughout the presentation, in order to further clarify the challenges that exist for clinicians with respect to the detection and comprehensive management of these individuals.

Learning Objectives

- Understand the current epidemiology of ADHD and comorbid depressive and anxiety disorders.
- Recognize overlapping symptoms that present in these comorbid populations, in order to achieve early and accurate detection.

Literature References

- Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, et al.: The prevalence and correlates of adult ADHD in the United States: Results from the National Comorbidity Survey Replication. American Journal of Psychiatry 2006; 163(4):716-623.
- McIntosh D, Kutch S, Binder C, Levitt A, Fallu A, Rosenbluth M: Adult ADHD and comorbid depression: A consensus-derived diagnostic algorithm for ADHD. Neuropsychiatr Dis Treat 2009; 5:137-150.

UNDERSTANDING THE NEUROBIOLOGY OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AND COMORBID DEPRESSION AND ANXIETY

Martin Katzman, START Clinic for Mood and Anxiety Disorders

Individual Abstract As the prevalence of Attention Deficit Hyperactivity Disorder (ADHD) is steadily increasing, it is essential to understand the implications it places on the individual, specifically in regards to cognitive functioning. Cognitive dysfunction resulting from ADHD and comorbid depressive and anxiety disorders often hinders executive functioning, memory, metacognitions, and maladaptive cognitions. Clinicians are often challenged when attempting to determine the origin of each disorder as a result of these cognitive impairments. Scientific research has demonstrated that the prefrontal cortex, caudate, and cerebellum are all implicated in the etiology of cognitive dysfunction in the ADHD clinical population. Emphasis will be placed on the neurobiology of ADHD both independently, as well as in conjunction with comorbid depressive and anxiety disorders. Clinical and diagnostic techniques will be discussed in order to increase awareness regarding these comorbid disorders, as well as to determine optimal treatment outcomes for patients.

Learning Objectives

- Understand the neurobiological correlates associated with ADHD and comorbid depressive and anxiety disorders.
- Recognize the functional impairments associated with cognitive dysfunction in order to accurately detect and treat the disorders.

Literature References

- Emond V, Joyal C, Poissant H: Structural and functional neuroanatomy of attention-deficit hyperactivity disorder (ADHD). Encephale 2009; 35(2):107-114.
- Roth RM, Saykin AJ: Executive dysfunction in attention-deficit/hyperactivity disorder: cognitive and neuroimaging findings. Psychiatr Clin North Am 2004; 27(1):83-96.

UPDATE: OUTCOMES OF RECENT NIMH MULTISITE RCTS IN GERIATRIC MOOD DISORDERS

Charles Reynolds, University of Pittsburgh School of Medicine Department of Psychiatry

Overall Abstract This panel will feature three NIMH sponsored multisite clinical trials in geriatric psychopharmacology. The first speaker will be Dr. Robert Young, Professor of Psychiatry at Weill Cornell School of Medicine, who will present the results of a comparative efficacy trial of lithium carbonate and divalproex in older adults with mania. The second speaker will be Dr. Barnett Myers, Professor of Psychiatry at Weill Cornell, who will present the results of the STOP-PD study of the acute treatment of psychotic depression, together with the design and methodology of an ongoing continuation trial (a double-blind discontinuation trial of adjunctive antipsychotic pharmacotherapy in participants who have responded to the combination of antidepressant medication and antipsychotic medication in midlife and older adults. Finally Dr. Jordan Karp, Associate Professor of Psychiatry at the University of Pittsburgh, will speak about his multi-site clinical trial in treatment resistant nonpsychotic, non-bipolar depression in older adults, using adjunctive buprenorphine. As a background for his talk, Dr. Karp will briefly summarize the results of the recently completed, NIMH sponsored IRL GREY, study, which examined the efficacy of augmenting venlafaxine with aripiprazole in treatment resistant late life depression. Dr. Charles Reynolds, UPMC Endowed Professor of Geriatric Psychiatry, will serve as discussant and moderator of the panel.

Learning Objectives

- Following the presentation, participants will be able to specify evidenced-based advances in treatment of geriatric bi-polar disorder, psychotic disorder and treatment resistance depression in older adults.
- Following the presentation, participants will be able to discuss the complexities of conducting RCTs in older adults with respect to issues such as medical co-morbidity and cognitive impairment.

LITHIUM AND DIVALPROEX IN THE TREATMENT OF MANIA IN OLDER PATIENTS WITH BIPOLAR DISORDER: A RANDOMIZED CLINICAL TRIAL

Robert Young, Weill Cornell Medical College

Individual Abstract Objectives/Content: Despite the increasing number of elders with bipolar disorder (BD), there have been no published randomized controlled trials to guide treatment of late-life mania. We compared the tolerability and efficacy of lithium carbonate (LI) and divalproex sodium (VAL) in older adults with bipolar mania. We hypothesized that VAL would be better tolerated and more efficacious than LI.

Methods: We conducted a randomized, double-blind acute treatment study at academic psychiatric inpatient and outpatient services. The subjects were aged > 60 years, had BD type I, and presented with a manic, hypomanic or mixed episode. Participants were randomized under double-blind conditions to LI (target serum concentrations: 0·80-0·99 mEq/L) or VAL (target: 80-99 mcg/ml) for 9 weeks. Participants with inadequate response after 3 weeks received open adjunctive risperidone. Tolerability was assessed based on a measure of sedation and on the proportion achieving target concentrations. Efficacy was assessed with the Young Mania Rating Scale (YMRS).

Results: Among the randomized participants (n= 224) attrition rates were similar for LI and VAL. The groups did not differ in terms of sedation. A similar proportion of participants achieved target concentrations. A longitudinal mixed-model of symptomatic improvement (YMRS change from baseline) statistically favored LI at week 9. However, differences in response rates were not statistically significant. Although patients with psychotic features were not excluded, the need for adjunctive risperidone was low and similar for LI and VAL.

Discussion: Clinicians and investigators should bear in mind the role of classical mood stabilizers, and particularly LI, in the management of older patients with BD.

Supported by National Institutes of Health U01MH068847, U01MH074511, U01 MH068846, R01 MH084921, P30 MH071944, P30 MH085943, P30 MH90333, P30 MH068638, K24 MH069430 and K02 MH067028, and by UL1 RR024996, and UL1 RR024989 from the US Public Health Service. Janssen Pharmaceuticals provided risperidone to some sites.

Learning Objectives The presentation will provide participants with:

- Findings from an NIH-funded randomized, double-blind controlled trial comparing lithium and divalproex in older adults with bipolar manic states.
- The limited existing evidence regarding mood stabilizer treatment of bipolar disorder in old age, and the implications of these findings for practice and further research.

Literature References

- Young RC, Mulsant BH: Bipolar Disorders in Late Life, in ASCP Model Psychopharmacology Curriculum. Edited by Osser DN, Glick ID, et al. 8th edition (in press).
- Forester B, Gildengers AG, Young RC: Biological factors in bipolar disorders in, Bipolar disorder. Basic mechanisms and therapeutic implications late life. Edited by J Soares, A Young, New York: Cambridge U. Press, 3rd ed. (in press).

THAT NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH) STUDIES OF THE ACUTE AND CONTINUATION PHARMACOTHERAPY OF PSYCHOTIC DEPRESSION (STOP PD I AND II)

Barnett Meyers, Weill Cornell Medical College

Individual Abstract Background: Psychotic major depression is a severe, highly recurrent disorder that Is associated with poor outcomes, including higher rates of relapse/recurrence, disability, and both mortality and suicide than occurs in nonpsychotic depression. Although expert guidelines recommend either electroconvulsive therapy or pharmacotherapy combining an antidepressant with an antipsychotic, there have been few pharmacotherapy trials using contemporary agents. Furthermore, there are no published pharmacotherapy studies that include the broad age range of patients needed to determine whether age influences efficacy or tolerability of intensive combination pharmacotherapy. STOP PD I was a double-blind placebo controlled trial that assessed the efficacy of combining sertraline (target doses 150-200 mg/day) and olanzapine (target doses 10-20 mg/day) compared to an olanzapine plus placebo control. STOP PD I participants covered a broad age range to assess the effect of older age on both treatment response and side effects during twelve-weeks of acute treatment. Results from STOP PD I demonstrated the efficacy of combination treatment without an age effect. Metabolic side occurred across the age spectrum of participants but more weight gain occurred in younger adults. (Meyers et. Al. Archives of General Psychiatry, 2009).
Objective: STOP PD II is an ongoing double-blind placebo-controlled trial that assesses the benefits versus risks of thirty-six weeks of continued combination treatment in a new cohort of acute phase remitters. The relapse prevention efficacy and metabolic risks of continued combination treatment are assess by comparing the course of monotherapy subjects to those who continue combination treatment. The moderating effect of specific gene associated with weight and metabolic abnormalities in population studies will be explored in olanzapine subjects. A supplemental neuroimaging RO1 (Aristotle Voineskos, PI) will use the long-term placebo-controlled double blind design to determine effects of extended olanzapine treatment on specific brain structures, networks, and functioning.
Results: STOP PD I results that comprise the basis for the current continuation/maintenance study will be reviewed. The acute phase treatment response of combination subjects under the double blind condition of STOP PDI will be compared to the response during the open label lead-in of STOP PD II. We will also present recently analyzed data on the post-remission course among remitters in STOP PD I who continued their acute phase treatment for an additional three months. Finally, we will report results using the recently developed Psychotic Depression Assessment Scale (PDSA) (Soren Ostergaard). The PDAS, which was empirically derived from Hamilton Depression and Brief Psychiatry Rating scales, quantifies changes in the severity of both affective and psychotic symptoms in psychotic depression.

Learning Objectives

- Attendees will become knowledgeable about the acute treatment options associated with remission of psychotic depression;
- Attendees will learn about how old age affects treatment response of psychotic depression;
- Attendees will become knowledgeable about risk versus benefit considerations in deciding the long-term management of psychotic depression.

Literature References

- Østergaard SD, Meyers BS, Flint AJ, Mulsant BH, Whyte EM, Ulbricht CM, Bech P,Rothschild AJ; STOP-PD Study Group. Measuring treatment response in psychotic depression: the Psychotic Depression Assessment Scale (PDAS) takes both depressive and psychotic symptoms into account. J Affect Disord. 2014 May;160:68-73. doi: 10.1016/j.jad.2013.12.020. Epub 2014 Jan 2. PubMed PMID:24439830; PubMed Central PMCID: PMC3981944.
- Meyers BS, Flint AJ, Rothschild AJ, Mulsant BH, Whyte, EM, Peasley-Miklus C, Papdemertiou E, Leon AC, Heo M: A double-blind randomized controlled trial of olanzapine plus sertraline vs. olanzapine plus placebo for psychotic depression: The Study of Pharmacotherapy of Psychotic Depression (STOP-PD). Arch Gen Psychiatry. 2009;66(8):838-47.

GETTING TO REMISSION IN LATE-LIFE DEPRESSION: RECENT RESULTS AND NEW DIRECTIONS

Jordan Karp, University of Pittsburgh

Individual Abstract Major Depressive Disorder (MDD) is common in older adults, leading to disability, suicidality, and increased mortality. A major problem with getting to remission is treatment-resistance to first-line therapies: 55-81% fail to remit with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI). Unlike younger adults there is little evidence from controlled trials about the benefits and risks of such treatments in older adults to guide second-line or augmentation pharmacotherapy.
I will first describe results from an NIMH-sponsored, multi-site, placebo-controlled, randomized clinical trial to test the efficacy and safety of aripiprazole augmentation for older adults with treatment-resistant depression. We treated 468 participants aged 60 and older with current major depressive episode, using venlafaxine extended-release (ER); 181 did not remit and were then randomized to 12 weeks of double-blind augmentation with aripiprazole or placebo. We measured efficacy in bringing about remission and resolution of suicidal ideation, and assessed safety and tolerability with cardiometabolic and neurological measures. Older adults on aripiprazole had a higher remission rate, compared to those on placebo (44% versus 29%; odds ratio [OR]=2.6, 95% CI 1.3-5.1, p=0.007; number needed to treat [NNT]=6.6 [95% CI 3.5-81.8]). Remission was stable during 12 additional weeks of continuation treatment. Additionally, the resolution of suicidal ideation was more marked with aripiprazole than with placebo (p=0.02). Akathisia was the most common adverse effect (27% of participants on aripiprazole).

Aripiprazole was not associated with an increase in adiposity compared to placebo. Aripiprazole was associated with more Parkinsonism but not with tardive dyskinesia, treatment-emergent suicidal ideation, QTc prolongation, or increases in glucose, insulin, or lipids. Our interpretation is that in older adults who fail to achieve remission from depression with a first-line antidepressant, the addition of aripiprazole is effective in achieving and sustaining remission. Tolerability concerns include potential for akathisia and Parkinsonism.
I will then describe the rationale and design of our ongoing successor study. This project is a multisite, placebo-controlled RCT comparing augmentation pharmacotherapy with low-dose buprenorphine for older adults with MDD who do not respond to optimized treatment with venlafaxine ER. Buprenorphine is a partial mu opiate receptor agonist and a kappa opiate receptor antagonist. The kappa antagonism is postulated to have an antidepressant effect. Using PET, fMRI, and rTMS, we are probing the binding, functional, and molecular effects of buprenorphine, assessing clinical outcomes, and probing the opiate and reward systems in the depressed aging brain. Our multiplex approach is an example of integrating measures of target engagement into clinical trials.

Learning Objectives

- Understand the efficacy and safety concerns of augmentation pharmacotherapy with aripiprazole in depressed older adults.
- Appreciate the role the opiate system may play in depression and its treatment.

Literature References

- Callahan CM, Kroenke K, Counsell SR, Hendrie HC, Perkins AJ, Katon W, et al. Treatment of depression improves physical functioning in older adults. J Am Geriatr Soc. 2005; 53(3): 367-73.
- Karp JF, Butters MA, Begley AE, Miller MD, Lenze EJ, Blumberger DM, Mulsant BH, Reynolds CF. Safety, tolerability, and clinical effect of low-dose buprenorphine for treatment-resistant depression in midlife and older adults. J Clin Psychiatry. 2014 Aug;75(8):e785-93.

10:45 a.m. - 12:15 p.m.
Panel Session

NEW FRONTIERS IN MEASUREMENT: THE REVOLUTION WILL BE PATIENT-CENTERED

Mark Opler, ProPhase, LLC

Overall Abstract As stated by Kuhn (1962), "the proponents of competing paradigms practice their trades in different worlds." At present, within mental health research, we have multiple competing paradigms of measurement, each with strengths and weaknesses. At present, the conventional approach to clinical outcome measures refined in the mid-late 20th Century, often with a categorical and diagnostically-narrow focus has begun to compete with new approaches, including performance based tests, novel domains of measurement, and expanded conceptual definitions of existing domains. The new imperative of effectiveness trials (Hogarty, Schooler and Baker, 1997; Hoagwood, 1995) also looms large, demanding evaluations that are more ecologically valid and meaningful to patients and caregivers. Additionally, conventional measures may be inherently incapable of detecting treatment effects based on novel mechanisms of action. As the demand for new measures increases, a framework for evaluating how new measurement tools are adopted should be developed. Measure selection processes must take ecological validity and contextual relevance into greater account, and assumptions about measures being "gold-standard" for certain types of trials must be challenged. Patient perspectives remain a vital component that has gone under-appreciated. The standards by which patients and clinicians define a treatment as "effective" are highly unlikely to be uniform (Kraemer et al 2011). In an effort to develop consensus on novel approaches to measurement, this workshop will include experts in measurement and psychometrics from academia, industry, and government bodies. Each will discuss different challenges in advancing measurement, challenging conventional approaches, and related issues. The session will cover the evolving views of existing domains (e.g. negative symptoms), evidence for the failure of conventional measures in studies of new mechanisms of action, and strategies for advancing measurement. Audience participation will be elicited through challenge questions and interactive, moderated question and answer sessions. By incorporating input from participants, the panel will conclude by summarizing recommendations and identifying actionable areas of consensus.

Learning Objectives

- To review and evaluate the evidence for "gaps" in conventional measurement, including categorical diagnostic schema versus dimensional approaches, performance of standard testing paradigms versus new modalities, and the need for measures to support trials of novel mechanisms of action;
- To identify barriers to adoption of new measures (e.g. validation) and develop strategies to help evaluate and select the appropriate tests for future clinical trials, including both efficacy and effectiveness studies.

CREATING AND USING "FIT FOR PURPOSE" CLINICAL OUTCOMES TO MEASURE CLINICALLY RELEVANT BENEFITS IN PSYCHIATRIC ILLNESSES

George Garibaldi, F Hoffmann-La Roche

Individual Abstract Outcome measures used in experimental trials aim at measuring the effect of a therapeutic intervention. Most of these outcomes were developed decades ago to validate the effect of therapies with older mechanisms of action. Further, little was done to understand the specific clinical relevance of these therapies to patients, clinicians and the society. There is a need to develop novel tools to measure the effects of innovative therapies on specific symptom domains and to evaluate the relevance of these effects to patients, clinicians and the society.
The proposed systematic approach includes 1) understanding the pharmacology of novel therapies and the expected clinical benefit on different symptom domains 2) exploring expectations from patients and their carers and 3) designing and validating outcome measures to evaluate the effectiveness of these novel interventions in patients with psychiatric disorders.
Examples of this approach are the "Patient Reported Troubling Symptoms" in major depressive disorders, the "Readiness for hospital Discharge Questionnaire" and "Readiness for Work" in schizophrenia.
Approaches for the identification, development and validation of "fit for purpose" novel outcome measures will be presented.

Learning Objectives

- Sharing the importance of defining the clinical relevance of a benefit associated with a therapeutic intervention.
- Understanding the methodology for the development and validation of novel clinical outcome measures.

Literature References

- Patient-rated troubling symptoms of depression instrument results correlate with traditional clinician- and patient-rated measures: a secondary analysis of a randomized, double-blind, placebo-controlled trial. Journal of affective disorders. 04/2009; 118(1-3):139-46.
- Psychometric evaluation of the Readiness for Discharge Questionnaire. Schizophrenia Research. 12/2005; 80(2-3):203-12.

ADVANCES IN NEGATIVE SYMPTOMS

Brian Kirkpatrick, University of Nevada School of Medicine

Individual Abstract The NIMH Consensus Development Conference on Negative Symptoms recommended the development of a new measure of negative symptoms that included five symptom domains and did not include items now known to be related to disorganization. The Brief Negative Symptom Scale (BNSS) grew out of that conference, and has shown excellent reliability and psychometrics in English, Italian, and Spanish versions; its performance in other languages is being evaluated. Of the multiple negative symptoms scales that have shown two factors--anhedonia/asociality/amotivation (AAA) and expressivity (blunted affect and alogia)--the BNSS has shown the clearest separation of these factors. The BNSS AAA factor, but not the expressivity factor, is a predictor of level of function. Data on the performance of the BNSS and the details of a training program will be presented.

Learning Objectives

- List the five negative symptoms domains recognized by the NIMH Consensus Development Conference on Negative Symptoms.
- Summarize the results of factor analyses of negative symptoms.

Literature References

- Strauss GP, Keller WR, Buchanan RW, Gold JM, Fischer BA, McMahon RP, Catalano LT, Culbreth AJ, Carpenter WT, Kirkpatrick B: Next-generation negative symptom assessment for clinical trials: validation of the Brief Negative Symptom Scale. Schizophr Res 2012; 142:88-92.
- Kirkpatrick B, Fenton WS, Carpenter WT Jr, Marder SR: The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull 2006; 32:214-9.

INDIVIDUALIZING AND INTEGRATING MEASUREMENT TOOLS FOR SOCIAL COGNITION

Anzalee Khan, ProPhase, LLC

Individual Abstract Over the past few years, there has been investigation into the psychological and neural substructures of social cognition in individuals with schizophrenia and related disorders. In individuals with these disorders, communication, the ability to relate to the mental state of others, identify or deduce intentions, or make decisions about emotional state, is a fundamental requirement of interacting. This talk offers a historical perspective on the methodological trajectory of social cognition. The speaker will discuss preliminary methodological issues and how it affects measurement.

At the current time, it is unclear how efficacious social cognitive measurements are. It is anticipated that over time, new measurements, interventions and understandings of social cognition will play a pronounced role combined with medication, social skills training, and cognitive remediation in focusing on the continuing challenge of improving outcomes in schizophrenia and related disorders. The following topics will be discussed:

i. The need for new measurements in social cognition;
ii. Correlates to negative symptoms as a functional outcome;
iii. Comparison of social cognitive mechanisms across disease areas;
iv. Findings using current measurement tools and new measurements focusing on dynamic targets and stimuli will be presented.

Learning Objectives

- The audience will gain knowledge on potential ways to measure social cognition, with focus on components of testing social cognition: (a) observing the patient with peers, across different aspects of the environment, (b) assessment tools, (c) interviewing clinicians about daily functioning.
- The audience will be able to understand that different disease areas have different constructs of social cognition that are prevalent, therefore one standard assessment tool needs to have a battery of tests that are applicable for different disease areas.

Literature References

- Lindenmayer JP1, McGurk SR, Khan A, Kaushik S, Thanju A, Hoffman L, Valdez G, Wance D, Herrmann E. Improving social cognition in schizophrenia: a pilot intervention combining computerized social cognition training with cognitive remediation. Schizophr Bull. 2013 May;39(3):507-17. doi: 10.1093/schbul/sbs120.
- Khan A, Lindenmayer JP, Gao L, Opler M. Social cognition and its correlates to functional outcomes in schizophrenia. European Psychiatry Volume 29, Supplement 1, 2014.

TRANSLATIONAL TARGETS FOR STIMULANT ADDICTION

Ivan Montoya, DHHS/National Institute on Drug Abuse

Overall Abstract Although approximately 1 million people seek treatment for stimulant (cocaine or methamphetamine) use disorders every year, and despite multiple therapeutic approaches investigated, there are no FDA approved medications to treat these disorders. Some of these approaches included compounds modulating dopamine, nicotinic, opioid, glutamate, and GABA pathways. More recent therapeutic strategies to treat stimulant use disorders include the use biologics such as vaccines, monoclonal antibodies, and enzymes aimed at limiting the access of stimulants to the brain. The purpose of this symposium is to highlight some promising pharmacological approaches for stimulant use disorders in the continuum of translation from basic to clinical research. The symposium will include presentation of serotonin 5-HT2C receptor ligands including lorcaserin (recently approved to treat obesity), orexin receptors antagonists, and summary of results of a proof-of-concept study with a genetically engineered butyrylcholinesterase for the treatment of cocaine addiction. It is expected that at the end of the symposium participants will gain knowledge about these new translational therapeutic targets and approaches for stimulant use disorders.

Learning Objectives At the end of the symposium, participant will:

- Gain knowledge about new translational therapeutic targets for stimulant addiction.

- Learn the recent advances in the development and evaluation of 5HT2c ligands, orexin receptor antagonists, and a genetically engineered butyrylcholinesterase.

USING X-RAY STRUCTURES OF THE OREXIN RECEPTORS TO DESIGN NEW DRUGS FOR THE TREATMENT OF COCAINE ADDICTION

Fiona Marshall, Heptares Therapeutics, Ltd.

Individual Abstract Cocaine abuse is considered to be one of the most serious problems in drug abuse with 11% of all patients over 12 years of age who enter drug treatment programs doing so for the treatment of cocaine addiction. Currently there are no FDA approved drugs for the treatment of cocaine addiction and the development of efficacious, safe drugs is a societal priority. The orexin system and in particular the G protein coupled receptor OX1 has been shown in animal models to play a pivotal role in regulating reward mechanisms and in particular through effects on drug seeking and craving. We are using a unique structure based drug discovery approach which is aimed at finding highly selective OX1 receptor antagonists for the treatment of cocaine addiction. We have solved the X-ray structures of the OX1 and related OX2 receptors and have used these to identify highly novel small molecule OX1 antagonists. These are being optimised for selectivity over OX2 which would results in sedative side effects. We will review the evidence for OX1 in addiction, present an overview of our program and the plan for translational studies to progress these compounds to the clinic.

Learning Objectives

- Review the rational for a role of orexin 1 antagonists in drug addiction.
- Provide an understanding of how structure based drug discovery techniques can be used to design a selective OX1 antagonist for the treatment of cocaine addiction.

Literature References

- Hollander JA, Pham D, Fowler CD, Kenny PJ. Hypocretin-1 receptors regulate the reinforcing and reward-enhancing effects of cocaine. Pharmacological and behavioural genetics evidence. Front Behav Neuroscience 2012; 6, 47-52.
- Smith RJ, See RE, Aston-Jones Gm. Orexin /hypocretin signaling at the orexin 1 receptor regulates cue –elicted cocaine-seeking. Eur. J. Neuroscience 2009; 30, 493-503.

INTEGRATING SEROTONIN 5-HT2C RECEPTOR LIGANDS INTO THERAPEUTICS FOR COCAINE USE DISORDER

Kathryn Cunningham, University of Texas Medical Branch

Individual Abstract Cocaine use disorder continues to extract considerable personal, health and societal tolls in the U.S. The cycling course of cocaine intake, abstinence and relapse is tied to a multitude of behavioral and cognitive processes with impulsivity (rapid unplanned reactions to stimuli without regard for the consequences) and cue reactivity (attentional bias toward cocaine-associated cues) cited as two key phenotypes that set up vulnerability to relapse even years into recovery. Medications that suppress impulsivity and cue reactivity may provide value in enhancing abstinence following termination of cocaine use. The purpose of this presentation is to discuss the outcomes of preclinical and clinical studies to suggest that dampened signaling through the serotonin (5-HT) 5-HT2C receptor (5-HT2CR) neurotransmission underlies impulsivity and cue reactivity phenotypes. We propose that normalization of 5-HT2CR hypofunctionality in cocaine-exposed individuals is a promising pharmacological target to promote recovery in cocaine use disorder. Ongoing basic and clinical research will be described that support the use FDA-approved and new novel 5-HT2CR ligands for therapeutics in cocaine use disorder. These findings may ultimately translate into an FDA-approved medication for cocaine use disorder, and the advances will guide integration of this knowledge into the dominant theoretical constructs of addiction.

Learning Objectives

- Appreciate vulnerability factors that put individuals at risk for relapse in cocaine use disorder.
- Identify new opportunities to pursue therapy for cocaine use disorder by mining the serotonin system.

Literature References

- Anastasio NC, Stutz SJ Fox RG, Sears RM, Emeson RB, DiLeone RJ, O'Neil RT, Fink LH, Li D, Green TA, Moeller FG, Cunningham KA: Functional status of the serotonin 5-HT2C receptor (5-HT2CR) drives interlocked phenotypes that precipitate relapse-like behaviors in cocaine dependence. Neuropsychopharmacology 2014; 39:370-382
- Anastasio NC, Liu S, Swinford SE, Maili L, Hamon SC, Lane SD, Fox RG, Nielsen DA, Cunningham KA, Moeller FG: Variation within the serotonin (5-HT) 5-HT2C receptor (5-HT2CR) system aligns with vulnerability to cocaine cue reactivity: A translational approach. Translational Psychiatry 2014; 4:e369

GENETICALLY ENGINEERED BUTYRYLCHOLINESTERASE FOR THE TREATMENT OF COCAINE ADDICTION: RESULTS OF PH2 CLINICAL STUDY

Rom Eliaz, Teva Pharamceuticals

Individual Abstract Cocaine abuse and dependence are problems with devastating medical and social consequences, and currently there is no reliable means to treat cocaine addiction and rescue from cocaine overdose. Human plasma butyrylcholinesterase (BChE) is known to contribute to cocaine hydrolysis and has been considered for use in treating cocaine addiction. Efforts to improve the catalytic efficiency of this enzyme have led to a quadruple mutant fused to recombinant human serum albumin, Albu-BChE, which consistently demonstrated its potential therapeutic benefit in a series of pharmacology experiments. Albu-BChE shows ability to hydrolyze cocaine with 1000-fold increase in catalytic efficiency as compared to wild-type BChE. The mutant fused BChE prevented signs of cocaine toxicity as well as selectively abolished cocaine-induced "reinstatement" of drug-seeking behavior when administered to rats and monkeys before cocaine challenge. Ph2 data of clinical development of Albu-BChE to evaluate its potential in treating cocaine addiction in human will be discussed.

DEFINING TREATMENT TARGETS ACROSS THE DEPRESSION SPECTRUM

Philip Harvey, Miller School of Medicine, University of Miami

Overall Abstract Depression is multifaceted and has multiple variants. Depression occurs on its own, in conjunction with medical conditions, and with other-comorbidities. Treatment response in depression is less then full in the majority of cases with current treatments. Treatment resistant depression is a major public health problem and disability and cognitive deficits are present in many individuals with partial to complete treatment response. Psychotic features are present in a substantial proportion of people with depression, with targets for their treatment not clearly defined at this point.

This symposium will provide perspectives on treatment targets other than the typical monoamine targets of previous medication treatments. Presentations will focus on inflammation as a treatment target in treatment-resistant depression, the biological of cancer as a determinant of depression and means to target these biological processes, glucocorticoids as a treatment target in psychotic depression, and targting the neurobiology underlying cognitive impairments in depression. These presentations will adopt a perspective of defining newer treatment targets that are differentiated from monamine targets, with a goal of increasing treatment response of both mood symptoms and associated features of variants of depression (cognitive deficits, psychosis, and disability) with diverse etiologies. Finally, our discussant will discuss the pragmatics of implementing target focused interventions in meaningful phase III trials as well as the challenges associated in advancing to phase III from phase II with some of the interventions suggested (e.g., stem cell therapy).

Learning Objectives

- To clarify thinking about treatment targets for understudied and poorly responsive features of depression.
- To realistically consider the practicalities of implementation of therapeutics aimed at novel targets in meaningful treatment trials.

DEPRESSION AND INFLAMMATION

Charles Nemeroff, University of Miami Leonard M. Miller School of Medicine

Individual Abstract Proinflammatory cytokines play a major role in a variety of autoimmune conditions such as rheumatoid arthritis, psoriasis and inflammatory bowel disease but also in coronary artery disease, diabetes and cancer. These disorders are associated with high rates of comorbid depression, and depressed patients show marked increases in prevalence rates of many of these disorders. Moreover, there is increasing evidence that a sizeable percentage of patients with major depression exhibit laboratory indices of inflammatory disease. Thus, depressed patients exhibit increased plasma and CSF concentrations of inflammatory cytokines such as IL-6, TNFα, and increases in acute phase reactants such as C-reactive protein (CRP) and increases in chemokines and cellular adhesion molecules. There is a positive correlation between depressive symptom severity and plasma concentrations of inflammatory cytokines, and treatment-resistant patients exhibit the highest rate of inflammation among the depressed patient population. Administration of interferon alpha and other inflammatory cytokines produce many of the signs and symptoms of major depression. Taken together, these data suggests that depression, in part, is a pro-inflammatory disorder and that these pathophysioloical alterations may underlie the increased risk for cardiovascular disease and stroke observed in patients with mood disorders. This presentation will focus on novel treatment strategies for the subset of depressed patients who exhibit increased inflammation. This includes cytokine receptor antagonists and mesenchymal stem cell therapy.

Learning Objectives

- To increase the understanding of the role of inflammation as an etiological factor and treatment target in depression.
- To increase the understanding of the potential efficacy of interventions targeting inflammation for the treatment of depression.

Literature References

- Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, Haroon E, Miller AH. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry. 70:31-41. 2013.
- Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. J Affect Disord. 150:736-744. 2013.

MECHANISMS BY WHICH DEPRESSION CAN INCREASE OCCURRENCE AND RECURRENCE OF BREAST CANCER IN WOMEN

Marc Lippman, University of Miami Miller School of Medicine

Individual Abstract Dozens of observational studies have incontrovertibly shown that depression is associated with an increased risk of breast cancer [as well as other malignancies] as well as higher rates of recurrence. The explanations for this have remained obscure although the problem is highly significant in that up to 30% of women diagnosed with breast cancer also meet criteria for clinical depression. A series of studies have demonstrated that depression is associated with major changes in inflammatory cytokines including il-6,il-1b, tnf -a, and others. Recent investigations in both clinical breast cancer and models of breast cancer in animals have proven that more aggressive and metastatic tumors are associated with substantial increases in circulating concentrations of these and other cytokines. Furthermore, these circulating cytokines have been shown to be produced by breast cancers directly and furthermore they have been shown to induce a series of host effects most notably the recruitment of myelo-derived suppressor cells ceom the bone marrow to multiple tissue sites. These potently immunosuppressive cells are hypothesized to protect metastatic breast cancers from immune targeting as direct interference with their recruitment or function reduces metastases in models of disease. Thus it appears reasonable that the production of either identical or phenotypically equivalent cytokines in the setting of depression may augment or replace those produced by breast cancers themselves and thus contribute to disease progression. This raises the noteworthy possibility that successful treatment of depression - if associated with a lessening of inflammatory cytokines and the myelo-derived suppressor cells they recruit could have substantial clinical benefit - an hypothesis we are exploring in a prospective randomized trial in depressed breast cancer patients.

Learning Objectives

- To understand the specific role of inflammatory cytokines as a treatment target in depression associated with breast cancer.
- To understand possible direct treatments of inflammation as a factor to reduce depression and reduce risk for recurrence of malignancy.

Literature References

- Drews-Elger K, Iorns E, Dias A, Ward TM, Dean S, Clarke, Miller P, Campion-Flora A, Nava Rodrigues D, Reis-Filho JS, Rae JM, Thomas D, Berry D, El-Ashry D and Lippman ME. Infiltrating S100A8+ myeloid cells promote metastatic spread of human breast cancer and predict poor clinical outcome. Breast Cancer Research and Treatment 2014; 14: 41-59.

- Walker J, Hansen CH, Martin P, Symeonides S, RamessurR, Murray G, Sharpe M. Prevalence, associations, and adequacy of treatment of major depression in patients with cancer: a cross-sectional analysis of routinely collected clinical data. Lancet Psychiatry 2014; 1: 343 - 350.

MIFEPRISTONE PLASMA LEVELS AND CLINICAL RESPONSE IN PATIENTS WITH PSYCHOTIC DEPRESSION

Joseph Belanoff, Corcept Therapeutics

Individual Abstract Background/objective: Psychotic Depression (PD) is a severe form of Major Depressive Disorder with no FDA approved treatment. Patients with PD experience higher morbidity and mortality than other forms of depression. The majority of patients with PD have hypothalamic-pituitary-adrenal (HPA) axis dysregulation as evidenced by abnormal afternoon and twenty four hour cortisol release, and non-suppression on the Dexamethasone Suppression Test (DST). Mifepristone, an antagonist at the Glucocorticoid Receptor (GR) and Progesterone Receptor (PR), has been studied in patients with PD because of its GR antagonist properties. Earlier Phase II and III studies have led to varied clinical results. A consistent and robust association between mifepristone plasma levels and reduction of psychosis has been repeated across several studies. This relationship is described here and will include data from a recently completed phase III study enrolling 292 patients with PD.

Methods: Data was collected across 5 phase II/III studies enrolling approximately 1400 patients with a diagnosis of DSM-IV PD. Patients were treated for 7 days with either mifepristone or placebo, and followed for an additional 7 weeks. Trough plasma levels were drawn prior to the final dose of study drug. Receiver Operator Curve (ROC) analyses were performed on mifepristone trough plasma level data to identify the optimal value to discriminate responders from non-responders in the pooled data set. Response was defined as a 50% reduction in psychotic symptoms from baseline at study day 7 and 56.

Results: A plasma level threshold was identified by ROC methodology on a pooled dataset, and utilized to compare response rates of mifepristone treated PD patients in the high vs low mifepristone plasma level groups. Patients in the high plasma level group demonstrated higher rates of response than patients in the low plasma level group. Response rates by age group and other demographics were also evaluated.

Conclusions: It appears that mifepristone may have benefit in a subset of the PD population. Administration of short term mifepristone in this population was safe and well tolerated.

Learning Objectives

- An understanding of the glucocorticoid hypothesis in psychotic depression.
- An understanding of the findings of mifepristone treatment for the psychotic symptoms of psychotic depression.

Literature References

- DeBattista C, Belanoff JK, Glass S, et al. Mifepristone versus Placebo in the Treatment of Psychosis in Patients with Psychotic Major Depression. Biological Psychiatry. 2006;60:1343-1349.
- Blasey CM, Block TS, Belanoff JK, Roe RL. Efficacy and safety of mifepristone for the treatment of psychotic depression. J Clin Psychopharmacol. 2011;31:436-40.

TARGETING COGNITION FOR TREATMENT IN DEPRESSION

Philip Harvey, Miller School of Medicine, University of Miami

Individual Abstract Although impairments in cognition have long been known to be present in major depression, recent research has suggested that these impairments may be less strongly associated with depressed mood than previously believed. Recent studies have suggested that there are several different features of depression relevant to impaired cognition that are worth attention. These studies have found that: 1: cognitive deficits are common in patients whose depressed mood has improved; 2: subjective cognitive impairments are not well correlated with objective performance measures, both prior to entering treatment and after successful treatment of depression; and 3: several recent studies have suggested that newer antidepressants with additional mechanisms of action other than NE and 5-HT transport inhibition may lead to improvements in cognition that are more substantial than older treatments. These improvements are present in cases whose depressed mood fails to improve with treatment, suggesting direct treatment effects. The origin of impaired cognition in depression may be similar to that in other mood and psychotic disorders, suggesting that similar treatments may have efficacy. This presentation will describe the brain circuitry associated with cognitive impairments in depression, as well as describing how cognitive remediation and pharmacological interventions may work by targeting this circuitry. Additional targets may come from the research that has examined the effects of newer antidepressants on cognition, including pharmacological probes specifically targeting the sertonin 7 receptor and treatment with stimulant medications. Finally, the potential functional impact of targeting cognitive impairments in major depression will also be discussed.

Learning Objectives

- To understand the prevalence and course of cognitive deficits in schizophrenia in relation to mood symptoms.
- To understand possible treatment targets for cognition in depression, including brain circuits, novel neurotransmitter targets, and more general effects of simulant treatments.

Literature References

- McIntyre RS, Lophavern S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. Int J Neuropsychopharmacol 2014; 17:1557-1567
- Keefe RS, Fox KH, Davis VG, Kennel C, Walker TM, Burdick KE, Harvey PD. The Brief Assessment of Cognition In Affective Disorders (BAC-A):performance of patients with bipolar depression and healthy controls. J Affect Disord. 2014;166:86-92

THE CHALLENGES OF SOCIAL CONNECTEDNESS FOR ADOLESCENTS WITH AUTISM SPECTRUM DISORDER: IMPLICATIONS FOR RESEARCH AND INTERVENTION

Michael Murray, Penn State Milton S. Hershey Medical Center

Overall Abstract Social skills deficits are the core impairment in autism spectrum disorder (ASD). Challenges with fluently decoding social information and executing appropriate responses become more impairing as individuals with ASD age given the increase in complexity of social interactions and the expectation of mastery of these skills. Adolescents are particularly vulnerable to struggle with social connectedness

with peers as their social environment rapidly changes with increased emphasis on social communication, both verbal and non-verbal, mediating these interactions.

Learning Objectives

- Understand the neural basis for the social processing challenges faced by adolescents with ASD.
- Understand novel therapeutic targets and interventions for improving these deficits.

INTRANASAL OXYTOCIN ENHANCES SOCIAL BRAIN CONNECTIVITY IN ASD

Allison Jack, Yale Child Study Center

Individual Abstract The hormone oxytocin (OT) plays an important role in regulating social affiliative and perceptual processes known to be impacted in ASD, and genetic variability in the oxytocinergic system has been linked to ASD susceptibility. Burgeoning interest in the use of intranasal OT administration as a pharmacological intervention for ASD makes it critical to understand the functional impacts of OT on neural systems supporting social perception. Using a randomized, double-blind, placebo-controlled crossover design, we examined the effects of intranasal OT on brain response to social stimuli among children with ASD.

Learning Objectives Participants will learn about:

- The nature of oxytocin effects on brain connectivity in ASD, the contexts in which these effects occur, and implications of this contextually specific action for therapeutic use of intranasal oxytocin.
- Person-specific factors that moderate oxytocin effects in ASD.

Literature References

- Jack A, Connelly JJ, Morris JP. DNA methylation of the oxytocin receptor gene predicts neural response to ambiguous social stimuli. Frontiers in Human Neuroscience. 2012;6:280. doi:10.3389/fnhum.2012.00280.
- Jack A, Morris JP. Neocerebellar contributions to social perception in adolescents with autism spectrum disorder. Developmental Cognitive Neuroscience. 2014; 10:77-92.

EFFECTS OF BETA-ADRENERGIC ANTAGONISM ON SOCIAL FUNCTIONING IN ASD

David Beversdorf, Center for Translational Neuroscience University Hospital

Individual Abstract ASD is characterized by impaired social communication and is often accompanied by anxiety. Propranolol has long been used for performance anxiety and public speaking anxiety. Single dose psychopharmacological challenges have demonstrated beneficial effects of propranolol on language tasks in ASD, and an uncontrolled case series in the past had also suggested effects on social behaviors. In a randomized, double-blind, placebo controlled crossover single dose psychopharmacological study, we examined the effects of propranolol on social interaction, and examined whether markers of anxiety were related to treatment response. Imaging correlates will also be discussed.

Learning Objectives Participants will learn about:

- The cognitive effects of propranolol, and application of this to ASD.
- Predictors and markers of treatment response.

Literature References

- Zamzow RM , Christ SE , Saklayen SS , Moffitt AJ , Bodner KE , Higgins KF ,Beversdorf DQ. Effect of propranolol on facial scanning in autism spectrum disorder: A preliminary investigation. Journal of Clinical and Experimental Neuropsychology. 36:4, (2014)
- Hecht PM, Will MJ, Schachtman TR, Welby LM, Beversdorf, DQ. Beta-adrenergic antagonist effects on a novel cognitive flexibility task in rodents. Behavioural Brain Research. 260:148-154 (2014).

EFFICACY OF THE MULTI-MEDIA SOCIAL SKILLS PROJECT FOR ADOLESCENTS WITH ASD

Michael Murray, Penn State Milton S. Hershey Medical Center

Individual Abstract Results of a large social skills intervention utilizing video modeling and peer generalization to improve social fluency, flexibility, and responsiveness for adolescents with ASD will be presented. Outcome measures included self-report, caregiver report, and behavioral observations. Patterns of response will be discussed.

Learning Objectives Participants will learn about:

- The efficacy of video modeling and peer generalization for social skills development.
- Predictors of response noted for improvement in target skills.

Literature References

- Pearl AM, Murray MJ, Smith LA, Arnold M. Assessing adolescent social competence using the Social Responsiveness Scale: should we ask both parents or will just one suffice? Autism, 2013, 17(6):736-42. doi: 10.1177/1362361312453349
- Murray MJ, Mayes SD, Smith LA. Brief Report: Excellent Agreement Between Two Brief Autism Scales (Checklist for Autism Spectrum Disorder and Social Responsiveness Scale) Completed Independently by Parents and the Autism Diagnostic Interview-Revised. Journal of Autism and Developmental Disorders. (2011) 41:1586-1590. DOI 10.1007/s10803-011-1178-0

2:00 p.m. - 4:00 p.m.
Pharmaceutical Pipeline Presentations

METADOXINE EXTENDED RELEASE (MDX): A NOVEL DRUG CANDIDATE FOR THE TREATMENT OF ADHD & FRAGILE X SYNDROME

Jonathan Rubin, Yaron Daniely
Alcobra, Ltd.

Abstract Metadoxine (pyridoxol L-2-pyrrolidone-5-carboxylate) is an ion-pair salt of pyridoxine (vitamin B6) and 2-pyrrolidone-5-carboxylate (PCA, also known as L-PGA). Metadoxine modulates GABAergic activity, and does not increase levels of brain neurotransmitters such as dopamine, norepinephrine and serotonin. In animal studies, Metadoxine has shown no signs of abuse or addiction potential. Metadoxine Extended Release (MDX) is a novel, immediate release and sustained release formulation in a bi-layer tablet.

Placebo-controlled studies of MDX in adults with ADHD produce a consistent signal of efficacy, and analysis of secondary endpoints and sub-scales suggest an impact on attention and cognitive function. No treatment-emergent serious adverse events or any meaningful differences in adverse events profile between the drug and placebo groups have been observed so far. A phase III 10-week, randomized, multicenter, placebo-controlled, double-blind, parallel group, study of MDX once daily in adults with ADHD was recently launched. The design of the study will be discussed.

Findings to date also suggest that MDX could improve attention and cognition in Fragile X Syndrome (FXS), a rare neuro-genetic disease and the most common inherited form of autism. Furthermore, pre-clinical studies in an animal model of Fragile X Syndrome demonstrated improvements in behavioral outcomes with metadoxine treatment.

A phase II 6-week, randomized, multicenter, placebo-controlled, double-blind, parallel group, study of MDX once daily in adults and adolescents with FXS was recently completed. Subjects had molecular confirmation of FXS (greater than or equal to 200 CGG repeats) and were between 14 and 55 years. The study was conducted at 12 sites in the US and 1 site in Israel. Results of this study will be presented.

Preclinical and clinical evidence demonstrates that MDX has a unique mechanism of action and consistent procognitive effects. Results from ongoing and recently completed studies in ADHD and FXS may provide important information about a novel and highly differentiated nonstimulant drug candidate.

Learning Objectives:

- Participants will learn about a new drug candidate, Metadoxine Extended Release (MDX), as a novel potential treatment for ADHD and;
- Participants will learn about the pharmacological profile of Metadoxine Extended Release (MDX), a monoamine-independent GABA modulator.

Prior publications / presentations

- Rubin J, et al. Metadoxine in ADHD and fragile X syndrome: a novel mechanism of action. Poster 1364 presented at: Society of Biological Psychiatry 69th Annual Scientific Meeting; May 10, 2014; New York, NY.
- Manor I et al. A randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy, safety, and tolerability of extended-release metadoxine in adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2012; 73(12):1517-1523.
- Manor I et al. Attention Benefits after a single dose of Metadoxine Extended Release in Adults with Predominantly Inattentive ADHD. Postgrad Med 2014; 126(5): 1-10.
- Adler L et al. Randomized Controlled Trials of Metadoxine Extended Release in Adults with Attention-Deficit/Hyperactivity Disorder. Symposium presented at AACAP 61st Annual Meeting; October 22, 2014; San Diego, CA.

DASOTRALINE: A NOVEL DRUG CANDIDATE FOR THE TREATMENT OF ADHD

Robert Goldman, Kenneth *S. Koblan, Seth C. Hopkins, Antony Loebel*
Sunovion Pharmaceuticals, Inc.

Abstract Several classes of drugs have demonstrated efficacy in the treatment of ADHD, including short- and long-acting stimulant and non-stimulant medications. However, there continues to be a need for additional treatment options that may offer a more differentiated clinical profile than current agents. Dasotraline [(1R,4S)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-amine], currently in development for adult and pediatric ADHD, is a potent inhibitor of human DA transporters (DAT; dopamine uptake IC50 3 nM) and NE transporters (NET; norepinephrine uptake IC50 4 nM), and a weaker inhibitor of human serotonin transporters (SERT; serotonin uptake IC50 15 nM; data-on-file, 2014). In humans, dasotraline has a tmax of 10-12 hours, a terminal elimination half-life (t½) of 47-77 hours, and achieves steady state plasma concentration by 2 weeks of daily dosing. A clinical trial has been completed in adults meeting DSM-IV-TR criteria for ADHD who were randomized, without titration, to 4 weeks of double-blind, once-daily treatment with fixed doses of dasotraline 4 mg/d (N=114), 8 mg/d (N=107), or placebo (N=110). On the ADHD Rating Scale, Version IV (ADHD RS-IV) total score, significant LS mean improvement was observed at Week 4 for dasotraline 8 mg/d versus placebo (-13.9 vs -9.7; P=0.019), with trend level significance for 4 mg/d (-12.4; P=0.076). LS mean improvement in a modified CGI-S scale was significantly greater at Week 4 for dasotraline 8 mg/d versus placebo (-1.1 vs -0.7; P=0.013), and for 4 mg/d (-1.1 vs -0.7; P=0.021). The most frequent adverse events reported were insomnia, decreased appetite, nausea, and dry mouth. The pharmacokinetic and pharmacodynamic characteristics of dasotraline suggest that it may have a favorable therapeutic profile for the treatment of ADHD, offering once-per-day dosing that provides sustained inhibition of DA and NE reuptake throughout the 24 hour dosing interval, with possible low risk of abuse potential due to its delayed tmax. The results of this first clinical trial provide preliminary evidence indicating that once-daily dosing with dasotraline, a long-acting, dual monoamine reuptake inhibitor, may be a safe and efficacious treatment for adult ADHD.

Learning objectives:

1. Participants will learn about the efficacy and tolerability of dasotraline in adult patients diagnosed with ADHD.
2. Participants will learn about the pharmacokinetic profile of a dasotraline, a new drug candidate for the treatment of ADHD.

DISCOVERY AND DEVELOPMENT OF EMB-001 FOR THE TREATMENT OF SUBSTANCE USE DISORDERS

Michael Detke[5], Nicholas Goeders[1], Glenn Guerin[1], Carol Gloff[3], Gary Connor[3], Doug Feltner[4]
[1]LSU Health Sciences Center, [3]Embera NeuroTherapeutics, [4]Embera NeuroTherapeutics, AbbVie Inc., [5]Embera NeuroTherapeutics, Indiana University School of Medicine

Abstract Background: EMB-001 is a combination of two FDA-approved drugs: metyrapone, a cortisol synthesis inhibitor, and oxazepam, a benzodiazepine. Metyrapone is approved for one day only as a test; oxazepam is approved for various anxiety disorders. We hypothesized that a combination of drugs working by different stress-related mechanisms may be useful for the treatment of substance use disorders, at doses that minimize the safety/tolerability risks of each individual drug.

Methods: We summarize a range of preclinical and clinical data supporting the potential utility of EMB-001 for the treatment of substance use disorders including a pilot human study in cocaine dependent subjects, including measures of cocaine use and craving. New safety data from a Phase 1 study will be available in time for the meeting.
Results: Metyrapone and oxazepam together reduce cocaine self-administration in rats at doses where each is ineffective alone (Goeders, 2008). A formal dose-finding study in rats confirmed the effective doses in EMB-001 are lower than the effective doses of each drug alone. EMB-001 also reduces nicotine self-administration in rats (Goeders, 2012), and attenuates cocaine and methamphetamine cue reactivity in rats (Keller, 2013).
In five trials, (O'Dwyer 1995; Murphy 1998; Eriksson, 2001; Jahn, 2004; Rogoz 2004) metyrapone was generally safe and well-tolerated at 500-4000 mg/day for 2-8 weeks. A human study of EMB-001 in cocaine dependence (Kablinger, 2012) showed a significant reduction in cocaine use and EMB-001 was generally well-tolerated.
Conclusions: Preclinical data demonstrate that EMB-001 is effective in several animal models of drug addiction. A pilot human study suggested efficacy in cocaine dependent subjects, with reduced cocaine use at endpoint. New data from a Phase 1 combined single/multiple ascending dose GCP-compliant study to assess safety will be presented, along with plans for Phase 2 efficacy studies in cocaine use disorder and tobacco use disorder.
No pharmaceutical treatments are currently available for cocaine use disorder, and treatments for tobacco use disorder are only effective approximately 25% of the time. This pharmacological intervention has potential to treat methamphetamine use disorder as well, for which no FDA-approved treatments exist.

PH94B NASAL SPRAY AS A PRN TREATMENT FOR SOCIAL ANXIETY DISORDER: A PHASE 3 PILOT TRIAL

Michael Liebowtiz[1], *Ann Draine*[2], *Louis Monti*[3], *Rita Hanover*[4]
[1]*Columbia University,* [2]*Medical Research Network,* [3]*Pherin Pharmaceuticals,* [4]*Westport Compass*

Abstract Social Anxiety Disorder (SAD) is a prevalent anxiety disorder that is often chronic and disabling. Several medications have been approved for this condition, but they require sustained treatment, are of limited help for many affected individuals, and often have troubling side effects. Cognitive behavior therapy (CBT) is also helpful but many individuals do not participate or fully benefit.
Given the predictable occurrence of the performance and social encounters many individuals with SAD dread and avoid, an effective rapidly acting treatment for the symptoms of SAD that could be used just before such events could be highly useful. PH94B is a synthetic neurosteroid developed by Pherin Pharmaceuticals that is delivered intranasally in low microgram doses and acts via nasal chemosensory receptors to rapidly affect brain structures such as hypothalamus, amygdala, prefrontal cortex and hippocampus. We have previously presented data to show that PH94B rapidly and transiently relieved symptoms of generalized anxiety disorder (GAD). PH94B was also shown in a Phase 2 double blind placebo controlled trial to be significantly more effective than placebo in reducing public speaking and social interaction anxiety during clinic challenges of individuals with SAD. The next logical step was to ascertain whether PH94B would be reduce public speaking and social interaction anxiety and avoidance in people with SAD using the medication as needed in their daily lives. Given that prior clinical studies of PH94B involved only women, we also wanted to evaluate the effectiveness of PH94B in both sexes. Women were given the same dosage as used in our study, while men were given twice the dose.
The study reported here was a Phase 3 pilot/feasibility trial to test a methodology for comparing PH94B and placebo used on a PRN basis by individuals meeting DSM 5 criteria for SAD. Subjects meeting study inclusion and exclusion criteria carried a diary for 2 weeks during which they recorded any anxiety producing social or performance events, and rated the severity of their anxiety on the 0-100 SUDS scale. Those who met predetermined criteria for event frequency and severity were then randomized to 2 weeks of PH94B or placebo, used on a PRN basis up to 4 times per day. Subjects were instructed how to self-administer PH94B or placebo intranasally 15 minutes before entering a feared situation, and how to record both their anticipatory anxiety prior to the event and their peak anxiety during the event in their paper diaries. After 2 weeks, subjects were crossed over to the opposite treatment for an additional 2 weeks. During the trial subjects were seen weekly for ratings on the Liebowitz Social Anxiety Scale (LSAS) and CGI, and they also completed a patient global rating (PGI) and received new weekly diary forms and fresh bottles of medication.
The predetermined primary outcome measure was a within subjects comparison of mean peak SUDs for all events recorded during the 2 weeks on PH94B versus mean peak SUDS on placebo. Secondary outcome measures included total LSAS, PGI, CGI-S, CGI-I, HAMD-17 and HAM-A at the end of each treatment phase. When carry over effects between the two phases of treatment were observed, between groups comparisons were conducted using data from the first 2 weeks of treatment.
Thirty-one subjects were evaluated for the study, 23 were randomized to treatment, and 22 had sufficient exposure to both treatments to be included in efficacy assessments. The mean age of the 22 subjects was 40.2 years, the average age of onset of SAD was 10.3 years, there were 11 male and 11 female subjects, and their mean baseline LSAS total score was 98, indicating severe SAD symptoms.
The mean SUDS peak score for all patients receiving placebo was 58.4 vs 51.1 for PH94B, a difference of 7.3 points, which was statistically significant (paired t 3.09, p=.006) with an effect size of .658 (Cohen's D) in favor of PH94B. Drug superiority over placebo on peak SUDS was similar for males and females. There was a small carry over effect on this variable, such that PH94B followed by placebo showed a smaller difference in favor of drug than did placebo followed by PH94B. However, the carryover effect was not sufficient to nullify the overall significant difference between drug and placebo.
On several secondary endpoints such as the LSAS and the PGI, the carry over effect of placebo being more effective following PH94B than when given as a first treatment, resulted in no overall difference between drug and placebo. However, when only the first 2 weeks of treatment were compared in between subject's analyses, PH94B showed significant superiority to placebo on the LSAS and PGI. CGI-I, Ham D and Ham A differences were not significant between treatments.
Adverse effects were mild, and did not show drug placebo differences.
Overall, despite the small study size, PH94B showed superiority to placebo in the whole sample on the primary outcome measure, and on several important secondary measures using between subjects comparisons of the first 2 week data. In addition, male and female subjects seemed to both benefit from PH94B. The findings are important for several reasons. For one, if larger follow-up Phase 3 trials confirm our findings, PH94B could represent the first systematically studied PRN treatment for social anxiety disorder that could be used either as monotherapy, or if effective on further testing, as an adjunctive treatment. Secondly, if PH94B's effectiveness is confirmed, it would further validate the nasal chemosensory system as a novel pathway for administering medication.

THE ANTIDEPRESSANT ACTIVITY OF BASIMGLURANT, A NOVEL MGLU5-NAM; A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY IN THE ADJUNCTIVE TREATMENT OF MDD

Jorge Quiroz[2],Paul Tamburri[1], Dennis Deptula[2], Ludger Banken[3], Ulrich Beyer[3], Paulo Fontoura[3], Luca Santarelli[3]
[1]Roche, [2]Roche Innovation Center NY, [3]Roche Innovation Center Basel, Switzerland

Abstract Background: Therapies targeting the glutamatergic system are known to be efficacious in the treatment of mood disorders. Antagonism of the post-synaptic mGlu5 receptor is a novel approach to indirectly modulate glutamatergic (NMDA) function and has shown efficacy in a number of preclinical behavioral models of depression. Basimglurant is a potent and selective negative allosteric modulator of the mGlu5 receptor which has been comprehensively profiled in Ph1 and Ph2a trials. The main objectives of this Ph2b trial were to evaluate the safety and efficacy of basimglurant modified release (MR) vs. placebo, as adjunctive therapy to ongoing antidepressant treatment in patients with major depressive disorder (MDD) who showed inadequate response to at least one but no more than three treatment failures within the current episode.
Methods: In this 9-week study (6-week double-blind treatment, 3-week post-treatment follow-up), adult patients with DSM-IV-TR diagnosis of MDD were randomized to basimglurant 0.5 mg/d, 1.5 mg/d, or placebo (adjunctive to ongoing SSRI or SNRI). The primary endpoint was the mean change from baseline in the Montgomery-Åsberg Depression Rating Scale Sigma total score (MADRS), as rated by the clinician at week 6. Concomitantly, patient-rated MADRS scores were also collected and analyzed. Secondary endpoints included change in the Quick Inventory of Depressive Symptomatology (QIDS-SR16), MADRS response (≥ 50% reduction in score from baseline), MADRS remission (score of ≤ 10), and Clinician and Patient Global Impression scales (CGI-I, PGI-I and CGI-S). Exploratory endpoints included change in the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) and the Sheehan Disability Scale (SDS). Due to the exploratory nature of this study, one-sided p values were estimated with no adjustment for multiplicity. Completers (observed cases) ANCOVA and ITT MMRM statistical analysis were performed.
Results: 333 male and female patients were randomized in to the study. The primary endpoint for the study (clinician-rated MADRS) was not met (p=0.127 ITT MMRM analysis); a trend for improvement was observed for basimglurant 1.5 mg vs. placebo (p=0.061 completers ANCOVA analysis) while statistical significance was reached utilizing the patient-rated MADRS (p<0.025 in both analyses). Regarding the secondary endpoints basimglurant 1.5 mg showed significant improvements vs. placebo in QIDS mean change from baseline (p=0.004 in both analyses), CGI-I mean score (p<0.039 in both analyses), PGI-I mean score (p<0.029 in both analyses). Significant improvements were also seen with in the patient-rated MADRS remission rate (p<0.024 both analyses), and to a lesser degree in the patient-rated MADRS response (p<0.1 both analyses). Lastly, significant improvements were observed in the Q-LES-Q-SF (p=0.011) and the SDS items 2-3 (p=0.047) (ITT MMRM). Basimglurant dosed at 0.5 mg showed no benefit over placebo in any of these measures. Withdrawal rates due to adverse events were 5.4%, 7.2% and 4.5% for basimglurant 0.5 mg, 1.5 mg, and placebo, respectively. The most common adverse event was dizziness (4%, 23%, and 6%), mostly transient and of mild intensity. Mania (spontaneously resolved) lead to withdrawal of 2 patients from the study in the 1.5 mg arm.
Discussion: Adjunctive 1.5 mg/d basimglurant showed a consistent antidepressant effect across primary and secondary endpoints. Greater effects were seen in patient-rated endpoints such as the patient-rated MADRS and the QIDS, which statistically separated from placebo at several time-points including week 6, while clinician-rated MADRS only separated at earlier time-points but not at day 42. Basimglurant 0.5 mg/d was not effective compared to placebo. Study results should be considered in the context of the observed high placebo response in this trial (47% on the clinician-rated MADRS). Placebo response rates 40% have been reported as a threshold that impedes observing statistical separation for active arms in adjunctive MDD treatment trials, minimizing the possibility of detecting true antidepressant effects. In this trial, nevertheless, basimglurant 1.5mg response rates were still consistently superior to placebo. Furthermore, basimglurant was overall safe and well tolerated in combination with SSRI/SNRI with mild transient dizziness as the most common emergent adverse event. These results warrant further investigation of basimglurant in the treatment of MDD both in the adjunctive as well as monotherapy settings.

ADVANCING LOW FIELD MAGNETIC STIMULATION (LFMS), A POTENTIAL RAPIDLY-ACTING ANTIDEPRESSANT INTERVENTION

Atul Pande, Andrew Miller
Tal Medical

Abstract Low Field Magnetic Stimulation (LFMS) is a novel, non-invasive, neuromodulation technology being developed by Tal Medical. The mood elevating effect of LFMS were discovered serendipitously during proton echo-planar magnetic resonance spectroscopic imaging (EP-MRSI) study of bipolar depression patients, where patients reported mood improvement within minutes of exposure. This observation has been replicated and expanded to Major Depressive Disorder with two sham-controlled trials published previously (Am J Psychiatry 2004;161:93-98; Biol Psych 2014;76:186-93). The most recent trial was a double-blind sham-controlled trial study the effect of a single LFMS treatment in both MDD and Bipolar patients using a table top LFMS prototype device. Clinically meaningful mood improvement was observed following LFMS treatment relative to sham treatment for both diagnostic subgroups for the primary outcomes, the VAS and the HDRS-17 (3.1 point improvement over sham). Rapid improvement in mood was also observed using the Positive and Negative Affect Schedule (PANAS) scales as secondary measures. The time-varying magnetic field of LFMS induces a time-varying electric field in the brain. The electric field generated by the LFMS is much lower in magnitude (< 1 V/m) than the field used in repetitive transcranial magnetic stimulation (rTMS) treatment (> 100 V/m) and broadly extends throughout the cortex, unlike the more localized field used in rTMS. Importantly, LFMS does not directly induce the depolarization of neurons, unlike rTMS or ECT. There is no physical sensation associated with LFMS, which allows for robust blinding in clinical trials. Currently there is a 90 patient, multi-site clinical trial funded by the NIMH RAPID program ongoing which studies the effect of multiple LFMS treatments in MDD patients with a 4 week follow up period. Tal Medical is also launching a multi-site dose-optimization study of LFMS to investigate the effect of different LFMS treatment times and regimens.

A SINGLE INTRAVENOUS DOSE OF THE NMDA RECEPTOR GLYCINE SITE MODULATOR NRX-1074 DOSE DEPENDENTLY REDUCED DEPRESSION SCORES WITHIN 24 HOURS IN SUBJECTS WITH MAJOR DEPRESSIVE DISORDER (MDD)

Ronald Burch, Wen Yu, M. Amin Khan, Lee Bastin, Jeffrey Burgdorf, Joseph R Moskal
Naurex, Inc.

Abstract Background: NRX-1074 (threonyl-prolyl-2R-(2-benzyl)-prolyl-threonine amide) has the same tetrapeptide sequence as rapastinel (GLYX-13) except that the second Pro is benzylated. NRX-1074 is more potent in vitro, in animal models of antidepressant-like activity, NRX-1074 is more potent than GLYX-13 (100-fold) and orally active, and NRX-1074 does not exhibit a U-shaped dose-response like GLYX-13.
Methods: This randomized, double blind, placebo controlled study enrolled 142 subjects with MDD at 12 United States study sites. Subjects who were taking another antidepressant agent were required to discontinue all antidepressants for at least two weeks prior to receiving NRX-1074. Subjects received a single IV dose of placebo (N=52) or NRX-1074, 1 mg (23), 5 mg (54), or 10 mg (20), as monotherapy in order to determine the dose at which antidepressant activity is observed in order to provide pharmacokinetic-pharmacodynamic correlation to provide dose level guidance for oral administration. HDRS-17 and CGI-S scores, psychotomimetic effects (BPRS+), dissociative effects (CADSS) and other adverse events were monitored for 14 days.
Results: Demographics and baseline HDRS-17 (25.2-26.9) and CGI-S (4.4-4.6) scores were not significantly among treatment groups. NRX-1074 demonstrated a dose dependent antidepressant effect within 24 hours. In response to 10 mg, HDRS-17 declined 5.4 points compared to placebo (p=0.004) with an effect size of 0.7. CGI-S declined 0.9 points compared to placebo (p=0.0005). NRX-1074 did not induce significant changes in dissociative (CADSS) or psychotomimetic (BPRS+) scores. Adverse events were mostly mild to moderate with similar incidence to placebo and no discernible dose response.
Conclusions: A single IV dose of NRX-1074 induced a rapid and significant antidepressant effect with clear dose-response without dissociative or psychotomimetic side effects. NRX-1074 is undergoing repeat dose clinical trials using IV and oral dosing.

A RANDOMIZED PLACEBO-CONTROLLED ADJUNCTIVE TRIAL OF RILUZOLE IN TREATMENT-RESISTANT MAJOR DEPRESSIVE DISORDER

Sanjay Mathew[1], Maurizio Fava[2], Ralitza Guerguieva[3], Gerard Sanacora[3]
[1]Baylor College of Medicine, [2]Massachusetts General Hospital, [3]Yale Department of Psychiatry

Abstract Background: Preclinical studies have shown that riluzole, a FDA-approved drug for amyotrophic lateral sclerosis, modulates glutamate release and clearance, and has potent neuroprotective properties. Riluzole has shown antidepressant-like effects in rodent models used to screen for antidepressant activity. In addition, several small open-label clinical studies have suggested that riluzole has antidepressant and anxiolytic properties, even in patients resistant to conventional monoaminergic medications. The aim of this NIMH-sponsored collaborative study was to examine the antidepressant efficacy and safety of riluzole, by conducting the first double-blind, placebo-controlled trial of this agent in adults with major depressive disorder (MDD) who were inadequately responsive to antidepressant medication.
Methods: Patients were enrolled at three academic medical centers (Baylor College of Medicine, Massachusetts General Hospital, Yale University School of Medicine), with oversight by a NIMH Data Safety and Monitoring Board. Patients were between the ages of 18-65, met DSM-IV criteria for MDD, and had at least a moderate level of depressive severity, indexed by an Inventory of Depressive Symptomatology-Self Rated (IDS-SR) score of >20 and a Montgomery Asberg Depression Rating Scale (MADRS) score of 18 or higher. Exclusion criteria included patients with serious suicide risk, unstable medical illness, substance use disorders within the last 6 months, lifetime histories of bipolar disorder or psychotic disorders, and those who had failed to respond to 3 or more adequate antidepressant trials during the current major depressive episode. Patients meeting initial eligibility criteria were assigned to one of 2 groups (A or B), depending on whether they were receiving concurrent antidepressant treatment at Screening. MDD patients not taking an antidepressant (Group A) were given a 8-week prospective trial of open-label sertraline (flexibly dosed to 150 mg/day). Following the 8 week sertraline treatment period, Group A patients were eligible for a subsequent randomized, placebo-controlled double-blind phase if they continued to meet depressive severity thresholds and had < 50% decrease in the IDS-SR total score. Group B participants were individuals receiving an adequate dose of a SSRI, SNRI, or bupropion for at least 8 weeks, and were taking a stable dose for at least 4 weeks prior to randomization.
A sequential parallel comparison design was used for the 56 day double-blind, randomized adjunctive, placebo-controlled trial, which comprised two phases of approximately 28 days each. Patients were randomized to adjunctive treatment with either riluzole (50 mg BID) or placebo, with a 2:3:3 ratio for random assignment to the treatment sequences drug/drug, placebo/placebo, and placebo/drug, respectively. Clinical assessments were performed by trained raters every 7 days during the double-blind treatment period, followed by a 7 day taper period. The primary outcome was the change in the MADRS from baseline to the end of the double-blind treatment period. Secondary outcomes include the response rate, defined as at least a 50% improvement in MADRS compared to baseline. Safety and tolerability was assessed with the Systematic Assessment for Treatment Emergent Events (SAFTEE-SI).

Results: Enrollment occurred between June 2011 and December 2014, with the final study visit completed in February 2015. Across the three sites, 104 patients were randomized, and 85 patients completed the 8 week double-blind placebo phase. The database lock is scheduled for April 2015. The results of primary and key secondary analyses, including safety and tolerability information, will be presented.

Discussion: The implications of this study on research and clinical practice will be discussed. As riluzole is now available as a generic medication, a positive trial would support its broader use for difficult-to-treat depression and spur further investigations into mechanisms of action.
NCT01204918 Efficacy and Tolerability of Riluzole in Treatment Resistant Depression

A DOUBLE-BLIND, DOUBLY-RANDOMIZED, PLACEBO-CONTROLLED STUDY OF INTRANASAL ESKETAMINE IN AN ADAPTIVE TREATMENT PROTOCOL TO ASSESS SAFETY AND EFFICACY IN TREATMENT-RESISTANT DEPRESSION

Jaskaran Singh
Neuroscience, TA, JanssenR&D, LLC, Janssen Pharmaceutical Companies of JNJ

Abstract Background: Esketamine and ketamine have been shown to produce rapid antidepressant action in patients with treatment-resistant depression (TRD). The aim of the current study was to assess the efficacy, safety and dose response of intranasal esketamine in patients with TRD.
Methods: This was a 2-Panel, doubly-randomized, double-blind, placebo-controlled, multicenter study. Panel A was conducted in the United States and Belgium and Panel B is currently ongoing in Japan. In both panels, each subject participated in up to 4 phases: a screening phase of up to 4 weeks, a double-blind treatment phase which included two 1-week periods (Periods 1 and 2), a 9-week optional open-label treatment phase and an 8-week posttreatment follow-up phase. Only Panel A double blind phase data are available, and will be presented at this time.

The primary efficacy endpoint was the change from baseline to Day 8 in each period in the Montgomery-Asberg Depression Rating Scale (MADRS) total score combined. Safety and secondary efficacy endpoints were also assessed.
Results: A total of 67 subjects with TRD were randomly assigned in a 3:1:1:1 ratio to one of four treatment groups: placebo (n=33), esketamine 28 mg (n=11), esketamine 56 mg (n=11), or esketamine 84 mg (n=12) in Period 1. In Period 2, 28 placebo subjects who were eligible for re-randomization at the end of Period 1 were randomly assigned to placebo (n=6), esketamine 28 mg (n=8), esketamine 56 mg (n=9), or esketamine 84 mg (n=5) in a 1:1:1:1 ratio. Subjects were eligible for re-randomization if the patient-rated 16 item Quick Inventory of Depressive Symptomatology (QIDS-SR16) total score was ≥11 at the end of Period 1. The analysis of Period 1 and Period 2, combined using the weighted combination test, showed that the mean change in MADRS total score in all three esketamine groups was statistically superior to that obtained under placebo, based on a one-sided 0.05 significance level (p=0.021, p=0.001 and p<0.001 for esketamine 28 mg, 56 mg and 84 mg respectively). The mean differences (SE) from placebo (after one week of treatment) were -4.2(2.09) for esketamine 28 mg, -6.3(2.07) for esketamine 56 mg, and -9.0(2.13) for esketamine 84 mg. The magnitude of effect size in Period 1 increases from a low Cohen's D effect size in the 28 mg dose group (0.43) to a high Cohen's D effect size for the 56 (0.92) and 84 mg (1.19) dose groups.
The most common TEAEs during the double-blind phase (≥10% of subjects in any group) were: dizziness, dissociation, headache, dysgeusia, nasal discomfort, nausea, hypoaesthesia oral, dissociative symptoms, tunnel vision, oropharyngeal pain, throat irritation, blurred vision, hypersomnia, feeling abnormal, insomnia, hypertension, vertigo, polyuria and sedation. No death was reported. Transient elevation in blood pressure and heart rate was also observed on dosing days. The perceptual changes and dissociative symptoms measured by the Clinician administered Dissociative Symptom Scale (CADSS), suggest onset of these symptoms occurred shortly after the start of intranasal dosing and resolved by 2 hours postdose, and with repeated dosing these symptoms reduced significantly.
Conclusions: Intranasal esketamine administered in doses of 28, 56 and 84 mg across the study period showed statistically and clinically significant improvement of depressive symptoms in subjects with TRD, as demonstrated by the mean changes in the MADRS total score for the combined analysis of both periods. The doses evaluated were well tolerated and adverse events were similar to what has been observed previously with IV ketamine and eskatamine.

NON-INVASIVE NEUROMODULATION WITH TRIGEMINAL NERVE STIMULATION IN MAJOR DEPRESSIVE DISORDER AND OTHER CNS DISORDERS

Ian Cook[1], Andrew Leuchter[3], Christopher DeGiorgio[2]
[1]UCLA Semel Institute for Neuroscience and Human Behavior, [2]UCLA / NeuroSigma, [3]UCLA

Abstract Background: Modulation of brain activity via external Trigeminal Nerve Stimulation (eTNS) is an emerging therapy for CNS disorders, with an excellent safety profile and significant improvements in seizures, mood, cognition, and anxiety reported in preliminary open studies. Mechanistically, PET imaging findings showed acute, robust changes in cerebral perfusion in limbic and frontal regions. In a recently-completed dose ranging project, eTNS was examined under double-blind conditions in major depressive disorder (MDD) as an adjunct to pharmacotherapy.
Methods: Forty-three adults with MDD (age 23-65, avg 43.0 (11.5 sd), ATHF 1-10) completed at least six weeks of the trial (primary endpoint). Subjects stimulated the trigeminal nerve for 8 hours each night at home using custom patch electrodes placed on the forehead. Clinical outcomes were assessed with scales including the Beck Depression Inventory (BDI), Inventory of Depressive Symptomology (IDS-SR) and Hamilton Depression Rating Scale (HDRS17). Medications remained constant throughout.
Results: Symptom severity improved significantly for subjects receiving active stimulation (e.g., paired 2-tail t-test BDI 24.6 (8.5 sd) baseline vs 14.2 (7.3) week 6, p<0.00001). Subjects receiving active stimulation had significantly greater symptom improvement than subjects randomized to the control condition (e.g., BDI -41.7% vs -10.9% t=-2.61 2-tail p=0.013).
Conclusions: Significantly greater symptom reductions were achieved in the 6 weeks of acute eTNS treatment than in our control condition. These findings replicate open trial results, extend them under double-blind controlled conditions, and justify further development. Symptom improvement did not differ across stimulation frequencies ('doses'), suggesting that low doses of stimulation may lead to meaningful symptom improvement in MDD, and that the cumulative integration of stimulation events may be an important determinant of clinical effects. Trigeminal Nerve Stimulation is a unique form of neuromodulation because can be delivered at home using a non-invasive system, or may be deliverable with an implantable system that is under development. This novel approach to brain stimulation may have use as an adjunct to pharmacotherapy once efficacy and tolerability are confirmed with additional studies.

A DOUBLE-BLIND PLACEBO-CONTROLLED STUDY OF THE ANTIDEPRESSANT EFFECTS OF THE MGLU2 NEGATIVE ALLOSTERIC MODULATOR RG1578 IN PATIENTS WITH INADEQUATE RESPONSE TO ANTIDEPRESSANT THERAPY

Daniel Umbricht, Markus Niggli, Patricia Sanwald-Ducray, Dennis Deptula, Rema Moore, Waltraud Grünbauer, Lauren Boak, Silvia Gatti, Paulo Fontoura
F. Hoffmann-La Roche, Ltd.

Abstract Background: Abnormalities in glutamate transmission have been implicated in major depressive disorder (MDD). In particular, normal glutamate transmission may be disrupted via excessive autoinhibition through metabotrobic glutamate receptors type 2 (mGlu2). mGlu2 antagonists should correct this abnormal state and offer a therapeutic approach. We evaluated the antidepressant effects of the mGlu2 negative allosteric modulator RG1578 in patients with an inadequate response to SSRIs or SNRIs.
Methods: 310 patients with MDD and an inadequate response (inclusion criterion for severity of illness: MADRS ≥ 25, CGI ≥4) to up to two antidepressant trials were randomized to double-blind treatment and with placebo (N=86), 5 mg (N=89), 15 mg (N=88) or 30 mg (N=47) of RG1578 as an adjunct to ongoing treatment with an SSRI or SNRI. Patients completed 6 weeks treatment without major protocol violations The primary endpoint (MADRS) was assessed by fully blinded centralized raters. Secondary endpoints included the IDS-SR30, CPFQ, SDS and the CANTAB battery.
Results: At baseline the mean MADRS total score was 31 (□6 [SD]) and the CGI-S 4.4 (□0.7). At the end of treatment the decreases in the MADRS total score did not differ significantly between any active treatment arm and placebo (placebo: -11.8 □11.2; 5 mg: – 12.8□11.2; 15 mg: -11.8□11.2; 30 mg: -13.2□11.2). Response and remission rates did not differ significantly between treatment arms. Similar results were observed for all secondary outcome measures.

Discussion: Adjunctive treatment with RG1578 was not associated with significant antidepressant effects in patients with MDD and inadequate response to antidepressants.

ALKS 3831: A NOVEL DRUG CANDIDATE FOR THE TREATMENT OF SCHIZOPHRENIA

Elliot Ehrich, Mark Todtenkopf, Ying Jiang, Sanjeev Pathak, Anjana Bose, Daniel Deaver, Srdjan Stankovic, Bernard Silverman
Alkermes, Inc.

Abstract The biology of the strong association between many atypical antipsychotics and adverse weight gain and metabolic dysfunction has not been fully elucidated. The same could be said for the high rate of co-occurrence between schizophrenia and substance abuse. As a consequence, complexities of these associations present significant obstacles in the treatment and management of many patients with schizophrenia by limiting patient adherence and adversely impacting treatment outcomes.1,2 However, the role of the opioid system, specifically mu antagonism, for the treatment of substance abuse has been well established.3 As such, an antipsychotic designed to address these complexities through appropriate engagement of the opioid system and reward circuitry would present a substantive advancement in the treatment of schizophrenia.

Olanzapine (OLZ) is regarded as one of the most effective treatments for schizophrenia, but concerns with weight gain and adverse metabolic effects prevent its use as part of a first line treatment paradigm, which is of particular importance for the treatment of early psychotic episodes.1 Samidorphan (SAM), a novel opioid modulator, acts as an antagonist at mu opioid receptors. Nonclinical studies suggested that SAM may be useful in mitigating or preventing OLZ-induced weight gain. Using a standard rodent model, it was demonstrated that co-administration of SAM mitigated OLZ-induced weight gain, whereas naltrexone did not.4 In a subsequent study using non-human primates to investigate OLZ-induced changes in weight gain and metabolic effects, SAM attenuated OLZ-induced weight gain and fat accretion following 28-days of repeat daily dosing.5 .

Additionally, by virtue of its pharmacology, SAM may present additional benefits to patients with schizophrenia who have comorbid substance use disorder. Nonclinical studies have demonstrated that SAM, at doses that result in exposure similar to therapeutically relevant doses in humans, blocked mu-opioid agonist effects and reduced ethanol self-administration in rodents. In an early clinical study, it was found that SAM significantly reduced the event rate of heavy drinking compared to placebo in non-schizophrenic subjects.

ALKS 3831, a novel drug candidate, is a fixed-dose combination of OLZ and SAM currently under development for the treatment of schizophrenia. This formulation is intended to confer a more favorable safety profile compared to OLZ alone. To investigate the safety and effect on weight of ALKS 3831 in comparison to OLZ, a Phase I study in healthy, normal weight (BMI 18-25) male volunteers was conducted. This was a double-blind, parallel group design with daily dosing for 21 days. Subjects were randomized (n=106) to OLZ, ALKS 3831, SAM or placebo in a 2:2:1:1 ratio. Efficacy was determined by the mean change from baseline to last treatment period assessment in body weight (kg) for OLZ vs. ALKS 3831. After 21 days of daily dosing, the mean±SD change in body weight for OLZ and ALKS 3831 was +3.4±1.8 and +2.5±1.4, respectively. The weight gain observed in the ALKS 3831 group was significantly less than that of the OLZ group (p=0.014). Overall safety and tolerability of ALKS 3831 was similar to OLZ alone.

In a subsequent Phase 2 OLZ-controlled dose-ranging study, the safety, tolerability, and efficacy of ALKS 3831 was evaluated in adults with stable schizophrenia. Subjects were randomized in a 1:1:1:1 ratio to receive daily OLZ + placebo or 3 different ALKS 3831 treatment options (OLZ + 5, 10, or 20 mg SAM) in a double-blind paradigm following a 1-wk OLZ lead-in period. The primary efficacy endpoint was change in Positive and Negative Syndrome Scale (PANSS) total score from baseline to Week 12 to test equivalence of antipsychotic efficacy of the 3 pooled ALKS 3831 groups vs. OLZ. The analysis was performed for the full analysis set (FAS1) that included all randomized subjects who received ≥1 dose of study drug and had ≥1 post-baseline PANSS assessment. The pre-specified secondary endpoint, percent change in weight from baseline to Week 12 was evaluated in FAS1 (n=300) and the subset of subjects with observed weight gain during the 1-wk OLZ lead in period (FAS2, n=195). Safety and tolerability of ALKS 3831 relative to OLZ was also assessed. The change from baseline in PANSS total score with ALKS 3831 was equivalent to OLZ (LS mean difference±SE: 0.6±0.9; 95% CI: -1.2, 2.5). At Week 12, treatment with ALKS 3831 demonstrated a 37% lower mean weight gain vs. OLZ alone in FAS1 (p=0.006) and a 51% lower mean weight gain vs. OLZ in FAS2 (p<0.001). The risk of weight gain of ≥10% of baseline weight with OLZ was 2.7 times that of ALKS 3831 (95% CI: 1.1, 6.7; p=0.023) in FAS1 and 4.1 times that of ALKS 3831 (95% CI: 1.4, 12.3; p=0.008) in FAS2. The most common adverse events (≥5%) in the pooled ALKS 3831 subjects relative to OLZ subjects were somnolence, sedation, and dizziness. In this study, ALKS 3831 demonstrated efficacy equivalent to OLZ over the course of the 12-wk treatment. ALKS 3831 was associated with a clinically meaningful and statistically significant lower weight gain compared to OLZ alone. ALKS 3831 was well-tolerated with a safety profile similar to OLZ, with the exception of lower weight gain.

Evidence to date suggests that ALKS 3831 may represent a new advancement in the treatment of schizophrenia through maintaining benefits of the highly effective antipsychotic OLZ with an enhanced safety profile that addresses weight and metabolic liabilities. The potential utility of ALKS 3831 to treat patients with schizophrenia and co-occurring alcohol use disorder is the focus of an ongoing Phase 2 study.

References:

- Lieberman J, et al. N Eng J Med. 2005;353:1209-23.
- Gastfriend DR. Ann NY Acad Sci. 2014;1327:112-30.
- De Hert M, et al. World Psychiatry. 2011;10:52–77.
- Todtenkopf MS, et al. Neuropsychopharmacol. 2010:81.
- Todtenkopf MS, et al. Neuropsychopharmacol. 2011:206.

BREMELANOTIDE FOR HYPOACTIVE SEXUAL DESIRE DISORDER: ANALYSES FROM A PHASE 2B DOSE-RANGING STUDY

Anita Clayton[1], Carl Spana[2], Robert Jordan[2]
[1]University of Virginia, [2]Palatin Technologies, Inc.

Abstract Introduction: Bremelanotide (BMT) is a novel heptapeptide melanocortin-receptor-4 agonist. This study examined its subcutaneous self-administration by premenopausal patients with hypoactive sexual desire disorder (HSDD), female sexual arousal disorder (FSAD), or both, and included exploratory analyses specifically in subjects with HSDD.

Methods: Premenopausal women with HSDD and/or FSAD underwent a no-treatment diagnosis-confirmation month, followed by 4 weeks of single-blind, at-home placebo self-dosing (baseline). Subjects were then randomized to double-blind placebo or BMT 0.75, 1.25, or 1.75 mg self-administered for 12 weeks. Outcomes included changes from baseline to end of study in the number of satisfying sexual events (SSEs), Female Sexual Function Index (FSFI) scores, and Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) scores.
Results: Of 327 at-home study-drug users, 281 either had mixed HSDD/FSAD with a primary diagnosis of HSDD (n=206) or had solely HSDD (n=75). Among all 281 women, mean SSE change (per 4 weeks) was +0.2 for placebo, versus +0.8 for 0.75 mg, +0.7 for 1.25 mg, and +0.7 for 1.75 mg. Mean FSFI change was +1.55 versus +1.45, +3.11, and +4.24 for total score, and +0.37 versus +0.33, +0.58, and +0.97 respectively for desire subscore. Mean FSDS-DAO change was –6.6 versus –8.0, –9.6, and –12.7 for total score and –0.6 versus –0.5, –0.7, and –1.0 for Question 13 ("bothered by low desire"). On all outcomes, BMT benefit was statistically significant ($p < 0.05$, Van Elteren test) with the 1.75 mg dose.
Conclusions: In premenopausal HSDD, subcutaneous BMT yielded improvements across all key HSDD measures, with robust dose-dependence attaining statistical significance at the 1.75 mg dose.
Funding: Palatin Technologies, Inc.

4:15 p.m. – 5:30 p.m.
Special Session

PHARMACOLOGY-BASED NOMENCLATURE: AN INTERNATIONAL EFFORT
David Kupfer, University of Pittsburgh School of Medicine/Western Psychiatric Institute and Clinic
Joseph Zohar, Chaim Sheba Medical Center
Pierre Blier, University of Ottawa Institute of Mental Health Research
William Potter, National Institute of Mental Health

Overall Abstract Current psychopharmacological nomenclature remains wedded to an earlier period of scientific understanding, failing to reflect contemporary developments and knowledge, and it does not help clinicians to select the best medication for a given patient, and tends to confuse patients as they are being given a drug with a different name compared to their identified diagnosis (e.g., "antipsychotic" for depression). The Taskforce on Nomenclature, launched as an international effect by four colleges – the European College of Neuropsychopharmacology (ECNP), the American College of Neuropsychopharmacology (ACNP), the International College of Neuropsychopharmacology (CINP), and the Asian College of Neuropsychopharmacology (AsCNP) – to develop pharmacologically based principles for categorizing the most frequently used psychotropic drugs, completed its first phase in October, 2014. The project was initiated 5 years ago when representatives from the various neuropsychopharmacology organizations first met with a mission to update and improve mental health drug terminology.
A four-axis pharmacology-based nomenclature template for a current nomenclature uses contemporary scientific concepts of neuropsychopharmacology. The template comprises four axes: Axis 1: description of the pharmacologic target and mode of action (MOA); Axis 2: indication/what the drug is used for; Axis 3: description of the efficacy and major side effects; Axis 4: neurobiologic description. As part of the first phase of implementation, an English-language booklet, Neuroscience-Based Nomenclature (NbN), and a beta version App were released to ECNP 2014 attendees in October 2014.
This session will include an introduction of the overall plan and current advances which include the development of an App for the overall project (presenter: Dr. Joseph Zohar). Secondly, the "NbN" in action will be presented by Dr. Pierre Blier, who will utilize results of drugs exerting antidepressant action in demonstrating how the new nomenclature will work. Thirdly, Dr. David Kupfer will discuss next steps, particularly as it relates to needed changes in communication and language with a variety of organizations, journal editors, and clinicians. Dr. William Potter will be the discussant for this panel.

Tuesday, June 23, 2015

8:30 a.m. - 10:00 a.m.
REGULATORY PLENARY: FDA AND EMA APPROACHES TO INNOVATION IN CLINICAL TRIALS
Maurizio Fava, Massachusetts General Hospital
Tiffany Farchione, US Food and Drug Administration
Luca Pani, CHMP-EMA
Robert Temple, Food and Drug Administration

Overall Abstract This session will provide perspectives on methodological and design innovations from US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Dr. Tiffany Farchione, Deputy Director of the FDA's Division of Psychiatry Products (DPP) will discuss novel clinical endpoints. Specifically, she will discuss the review process for new clinical endpoints, both within and outside the qualification pathway. Dr. Luca Pani, Director General of the Italian Medicines Agency and member of the European Medicines Agency (EMA), will present an update on innovative conceptual approaches to clinical trial design and analysis both by the FDA and the EMA. New mechanisms of action and increasingly targeted therapies require innovation also in the design of clinical trials that should be reliable enough to support expedited development and authorization pathways for innovative drugs. New scientific and regulatory guidance is being drafted by FDA and EMA on aspects related to Adaptive Trial Design and study standardization, biomarkers in the early phase of development and surrogate outcome measures, clinical outcome assessments in the early phase of development, emerging technologies or new uses of existing technologies, innovative clinical trial design for pediatric therapeutics and risk-based monitoring of clinical trials. EMA is also working to be ready for the new scenario that will be introduced with the implementation of the new Clinical Trial Regulation that addresses the new scientific requirements, looking at the same time to create a favourable environment for innovative clinical trials in a global setting and to secure proper ethical considerations for all patient populations. Finally, Dr. Robert Temple, CDER's Deputy Center Director for Clinical Science and also Acting Deputy Director of the Office of Drug Evaluation I (ODE-I) at FDA, will review clinical trial design innovations and alternatives. There will be an informal discussion with the audience on these selected topics as well as other regulatory issues of common interest within this context.

1:00 p.m. - 2:30 p.m.

Panel Sessions

ADHD ACROSS THE LIFESPAN: EVIDENCE-BASED PRACTICES AND INVESTIGATIONAL APPROACHES

Jeffrey Newcorn, Icahn School of Medicine at Mount Sinai

Overall Abstract Background/Importance: ADHD is neurodevelopmental disorder which begins in childhood and often persists into adulthood. There are several FDA-approved stimulant and non-stimulant medications, and other medications are used off-label. There are also several evidence-based psychosocial treatments. Although the majority of individuals with ADHD are treated with stimulants and the effects are considered robust, improvement is greater for some outcomes than others, and time-action properties limit the consistency and duration of effects, even with long-acting formulations. Further, it remains uncertain whether stimulants improve long-term outcome. Therefore, developing new medications and/or methods of delivering existing medications is a high priority, and the development of alternative psychosocial or neurodevelopmental approaches is considered highly desirable. Purpose/Method: To review best practices in ADHD treatment from a variety of perspectives (e.g., pharmacologic, psychosocial, neurodevelopmental), highlighting strengths and weaknesses of each, the rationale for developing new interventions, and RCT data when available. Participants/Content: There will be 4 talks. 1) Ann Childress will discuss current best practices using stimulants, highlighting the rationale for developing new formulations despite the considerable success of existing treatments. She will describe several new methylphenidate and amphetamine formulations in development – discussing the rationale for each, how it might improve on existing treatments, and results of RCTS to date. 2) Dr. Newcorn will discuss current best practices with non-stimulants, discussing both monotherapy and combined treatment, comparative efficacy vs. stimulants, and relative advantages and shortcomings of existing medications. He will provide a mechanistically driven approach to identifying new non-stimulant medications, and discuss work in progress with several investigational products. 3) Jeffrey Halperin, PhD will discuss treatment in context of a neurodevelopmental model of ADHD, which emphasizes bidirectional influences between the child and his/her environment that promote or inhibit brain development, cognitive functioning and emotional self-regulation. He will provide a conceptual basis for developmentally-sensitive approaches using non-medication strategies - including aerobic exercise and cognitive enhancing interventions– and will discuss novel investigational approaches which aim to positively influence developmental trajectories in young children and limit adverse outcomes. 4) Anil Chacko, PhD will discuss recent trends in psychosocial interventions, including new approaches to behavioral management interventions (e.g., behavioral parent training; classroom contingency management), which consider alternative settings and treatment targets (e.g., improving peer friendships). He will discuss the results of RCTs examining the effects of cognitive training (e.g., parent-supported executive function training; neurofeedback, computerized cognitive training), exercise, and organizational skills interventions, and discuss potential issues, limitations and future directions for this work. Mark Stein PhD will serve as discussant, drawing from his expertise in the conduct of pharmacologic and psychosocial treatment trials, and discussing the potential role of investigational treatments in relation to key issues in clinical care.

Learning Objectives

- Attendees will understand current best practices using medications and psychosocial treatments for ADHD, and appreciate the need for new treatments and approaches to address limitations in existing treatments.
- Attendees will learn about the various pharmacologic and psychosocial interventions being developed for ADHD, and appreciate the potential role for each in the therapeutic armamentarium.

STIMULANTS: CURRENT BEST PRACTICES AND DRUGS IN DEVELOPMENT

Ann Childress, Center for Psychiatry and Behavioral Medicine, Inc.

Individual Abstract Objective: To discuss best practices for stimulant use in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) and data on drugs in development designed to address some of the limitations of currently marketed stimulants. Background: ADHD is a common neurobehavioral disorder beginning in childhood and often continuing though out the lifespan. Current guidelines recommend stimulants as first line treatment for ADHD and, for most patients, the response is compelling. However, symptom improvement is limited by onset and duration of action of stimulants and many patients continue to have significant impairment during the early morning while getting ready for school before the drugs take effect and after stimulants wear off in the evening. Multiple long acting formulations have been developed but many pose challenges for patients who have difficulty swallowing solid oral dosage forms. Methods: Current best practices for stimulant treatment of ADHD will be reviewed. To learn what stimulants are in development, Clinicaltrials.gov was searched on 28 Nov 2014 using the key word ADHD. A total of 867 studies were returned and reviewed. For new stimulant preparations, study sponsors were contacted to obtain further information and meeting abstracts and press releases were reviewed. Data from pharmacokinetic and efficacy studies will be described. Results: HLD200 is both a delayed and extended-release methylphenidate capsule and HLD100 is a delayed and extended release amphetamine capsule. Both are formulated to be administered in the evening with a delay of initial drug release of approximately 8 hours. Drug release then continues throughout the day and into the evening. Pharmacokinetic data for both compounds is consistent with drug design. Other formulations are in development for patients who have difficulty with or prefer not to take intact tablets or capsules. These include NT0102, an extended-release methylphenidate oral disintegrating tablet, NT0202, an extended-release amphetamine oral disintegrating tablet, TRI102, an amphetamine, and NWP09, an extended-release chewable tablet formulation of methylphenidate. A topical formulation, the d-amphetamine transdermal system (d-ATS), is also being studied. Pharmacokinetic data for NT0202 indicates that a 30 mg test dose was bioequivalent to a 30 mg dose of Mixed Amphetamine Salts Extended Release (Adderall XR). Press releases issued for NT0102 and D-ATS indicate that efficacy lasts through 12 hours after dosing. Conclusion: Several stimulant formulations are in development that may hold promise for patients who have difficulty ingesting their ADHD medication or have suboptimal symptom control during their morning routine and/or later in the day.

Learning Objectives

- Participants will learn current best treatment practices with use of stimulants.
- Participants will learn about unmet ADHD treatment needs and stimulants in development designed to address these issues.

Literature References

- Wolraich M, Brown L, Brown RT, DuPaul G, Earls M, Feldman HM, Ganiats TG, Kaplanek B, Meyer B, Perrin J, Pierce K, Reiff M, Stein MT, Visser S. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics2011 Nov;128(5):1007-22.
- Childress AC, Sallee FR. Attention-deficit/hyperactivity disorder with inadequate response to stimulants: approaches to management. CNS Drugs2014 Feb;28(2):121-9.

NON-STIMULANT MEDICATIONS: CURRENT BEST PRACTICES AND INVESTIGATIONAL DRUGS

Jeffrey Newcorn, Icahn School of Medicine at Mount Sinai

Individual Abstract Background/Importance: Stimulant medications have robust effects for ADHD symptoms and are generally recommended as first line in treatment algorithms. However, there are several FDA-approved non-stimulant medications, and others are used off-label. While non-stimulants have lower effect size than stimulants (Newcorn et al., 2008), they are relatively more useful for some indications (e.g., atomoxetine for ADHD + anxiety or substance abuse disorders, alpha-2 agonists for ADHD + tic disorders or aggression), and can be used to augment stimulant response or lower stimulant dose. Also attractive is the long duration of action. Nevertheless, owing to their relatively lower effectiveness, only a minority of youth are treated with non-stimulants as monotherapy. Given the societal imperative to decrease the use of controlled substances, development of more effective non-stimulants is highly desirable. Purpose/Method: To discuss best practices regarding use of non-stimulant medications, highlighting indications for which non-stimulants may be preferred as well as the data on which this is based, strengths and weaknesses of current medications, non-stimulants currently in development, and available RCT data. Content: Dr. Newcorn will discuss current best practices with atomoxetine and alpha-2 agonists, citing data regarding efficacy as monotherapy (both classes) and combined treatment (alpha-2 agonists), studies examining comparative efficacy of atomoxetine and stimulants, and relative advantages and shortcomings of these two medication classes. He will provide a mechanistically driven approach to identifying new non-stimulant medications, and discuss work in progress with several investigational products (e.g., metadoxine (pyridoxine + PGA), several mixed reuptake inhibiting medications (DA + NE, triple reuptake inhibitors), vayarin (omega fatty acids + phosphatidylserine), others). He will present results of clinical trials with metadoxine, vayarin and several of the novel mixed reuptake inhibiting compounds – all of which have separated from placebo. He will also discuss several medication classes that seemed promising based on mechanism of action and results of early proof of concept studies, which did not succeed in large-scale clinical trials. The discussion will be grounded in biological mechanisms of ADHD and potential drug targets. Discussion: Non-stimulant medications currently have an important role in ADHD treatment, though they are less effective than stimulants for core ADHD symptoms and are therefore used less often. Several investigational medications are currently in clinical trials, and initial results with several of these seem promising. However, none of the current investigational treatments is ready for "prime time."

Learning Objectives

- Attendees will understand current best practices using non-stimulant medications for ADHD, and appreciate the need for new treatments and approaches to address limitations in existing treatments.
- Attendees will learn about the various investigational non-stimulant medications currently being developed for ADHD, and appreciate the potential role for each in the therapeutic armamentarium.

Literature References

- Newcorn JH, Kratochvil CJ, Allen AJ, Casat CD, Ruff DD, Moore RJ, Michelson D; Atomoxetine/Methylphenidate Comparative Study Group. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. Am J Psychiatry. 2008 Jun;165(6):721-30.
- Manor I, Ben-Hayun R, Aharon-Peretz J, Salomy D, Weizman A, Daniely Y, Megiddo D, Newcorn JH, Biederman J, Adler LA. A randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy, safety, and tolerability of extended-release metadoxine in adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2012 Dec;73(12):1517-23.

NOVEL INTERVENTIONS FOR ADHD: CAN WE ALTER TRAJECTORIES TO IMPROVE LONG-TERM OUTCOMES

Jeffrey Halperin, Queens College, City University of New York

Individual Abstract Background/Importance: ADHD typically emerges during the preschool years and causes significant functional disability throughout the lifespan. Empirically-validated interventions have been shown to ameliorate the core symptoms of ADHD. However, gains are rarely maintained after the termination of treatment, and relatively few individuals with ADHD receive effective treatment throughout the full course of their disorder. Thus, currently-available treatments provide short-term symptomatic relief for ADHD, but limited, if any, long-term benefits for most affected individuals. As a result, many individuals with ADHD have poor long-term outcomes irrespective of whether they were effectively treated during childhood. Thus, the development of novel treatments that provide enduring therapeutic benefit by altering the chronic and oftentimes debilitating course of the disorder could have a huge impact.

Participants/Content: Initially, a model of ADHD pathophysiology which emphasizes bidirectional influences between children and their environment that promote or inhibit neurodevelopmental processes linked to the disorder will be presented. This model provides a conceptual basis for developmentally-sensitive intervention approaches which use non-medication strategies, including lifestyle changes that have the potential to alter the trajectory/course of ADHD and yield more optimal outcomes. Finally, data from studies that employ novel investigational approaches including cognitive enhancing interventions and aerobic exercise will be discussed. This field of research is still in its infancy – limitations, challenges, and directions for future research will be presented.

Learning Objectives

- To provide a developmental perspective on intervention such that the audience will understand the benefits of small but lasting changes in ADHD trajectory relative to larger acute improvements that may not endure over time.
- To provide the audience with an appreciation of the beneficial effects of physical exercise and cognitive training on brain growth and development, as well as the potential of these activities to have a positive effect on ADHD outcomes.

Literature References

- Halperin JM, Healey DM: The influences of environmental enrichment, cognitive enhancement, and physical exercise on brain development: can we alter the developmental trajectory of ADHD? Neurosci Biobehav Rev 2011; 35:621–634

- Halperin JM, Schulz KP: Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. Psychol Bull 2006; 132:560–581

NON-PHARMACOLOGICAL APPROACHES TO TREATING CORE SYMPTOMS AND RELATED IMPAIRMENTS IN YOUTH WITH ADHD

Anil Chacko, New York University

Individual Abstract Purpose & Content: Non-pharmacological approaches to treating the core symptoms of ADHD and related impairments have had increased empirical attention over the past decade given the sobering findings of the MTA study on the limited effects of most commonly used pharmacological and psychosocial interventions for ADHD on key areas of functioning and longer-term outcomes. This presentation will focus on a review of recent literature regarding these non-pharmacological interventions and future direction in this area of research.

Methods: A systematic review of the literature will be conducted, including a review of recent meta-analyses, of behavioral interventions (e.g., parent friendship coaching) and skills-based interventions (e.g., organizational skills training) to address key areas of functioning (e.g., peer relationship difficulties; academic functioning). Moreover, a review of recently completed "brain-training" interventions that attempt to alter underlying pathophysiology or compensatory mechanisms associated with recovery from ADHD will be reviewed.

Results: The recent literature on behavioral interventions and skills-based interventions offer considerable promise but issues regarding feasibility of these interventions in routine clinical practice may limit the potential impact of these interventions. To date, findings from randomized controlled trial of brain-training have suggested limited impact on core symptoms of ADHD and related impairments, particular in comparison to well-established pharmacological and behavioral interventions for ADHD. The presentation will conclude with future directions in non-pharmacological interventions for youth with ADHD, including investigating the effects of combining skills-based interventions with brain training approaches.

Importance: There has been considerable debate in the field regarding the efficacy of non-pharmacological approaches to treating ADHD in youth. Understanding what works for whom and for which outcomes is necessary to understand how best to provide treatment packages or algorithms for youth with ADHD that include non-pharmacological approaches. This presentation will provide the audience the foundation to consider such approaches in clinical practice and potential areas for further research.

Learning Objectives

- To understand the current state of the literature regarding the impact of novel approaches to behavioral interventions, skills-based training and "brain-training" for treating ADHD in youth.
- To understand the promise, limitations and future direction of these approaches as stand-alone interventions as well as the potential for combining these interventions to maximize outcomes for youth with ADHD.

Literature References

- Sonuga-Barke EJ, Brandeis D, Cortese S, et al. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. Am J Psychiatry 2013; 170; 275-289.
- Chacko A, Kofler M, Jarrett M. Improving outcomes for youth with ADHD: a conceptual framework for combined neurocognitive and skill-based treatment approaches. Clin Child Fam Psychol Rev 2014; DOI 10.1007/s10567-014-0171-5.

INFLAMMATION IN MOOD, SLEEP & OBESITY

Erika Saunders, Penn State College of Medicine

Overall Abstract Somatic symptoms of mood disorders may be related to biological mechanisms of stress and immune responses, including alterations in polyunsaturated fatty acids (PUFAs) and other inflammatory products. Here we discuss studies addressing the initial translation of these findings into biomarkers and therapeutic investigations 1) Increases in brain arachidonic acid (AA) metabolites derived from omega-6 linoleic acid are found in post-mortem studies of bipolar disorder (BD), and reversed in rodent studies of mood stabilizing medications. Baseline levels of plasma omega-3 eicosapentaenoic acid (EPA) were lower in acutely ill BD patients, during a depressive or manic episode, compared to healthy controls. After recovery the same BD patients exhibited increased omega-3 levels, though dietary self-report showed no difference in intake. Planned interventions to PUFA through diet to modulate AA and EPA will be discussed. 2) Weight regain is a major barrier for obesity management, and is thought to be influenced by psychoimmunological status. Cytokine profiles and depressive symptomatology were studied in obese patients before and after weight loss. Depression severity was associated with greater weight regain at 1-year post intervention. Higher TNFα levels after weight loss associated with lower weight regain, with this effect being more pronounced in men. The protective effect of TNFα on weight regain may be mediated by severity of depression, indicating that psychoimmunological state could be an important factor that informs course of treatment 3) Hyperactivity of the stress system is found in insomnia patients, while pro-inflammatory cytokines mediate daytime sleepiness and fatigue. Sleep/arousal biomarkers identify a phenotype of insomnia patients with objective short sleep duration who are at increased risk of morbidity independent of behavioral factors. Findings from a longitudinal cohort of young children followed-up as adolescents and young adults showed that this insomnia phenotype is associated with increased cortisol levels and pro-inflammatory cytokines. Pilot work indicates that a sedative antidepressant decreases cortisol levels in patients with insomnia, whereas cognitive-behavioral treatment does not. New pharmacologic agents should target the underlying mechanisms of biologically severe insomnia. 4) Inflammation occurs in major depressive episodes, and new data indicate that peripheral inflammatory biomarkers (adipokines, acute phase proteins, and cytokines) can subtype individuals who will respond to anti-inflammatory treatment. Combinatorial measures of inflammation identify a subset of patients with major depressive disorder who will respond positively to omega-3 EPA-enriched dietary monotherapy, versus placebo and dietary docosahexaenoic acid (DHA). Collectively, this shows that lipid and inflammatory markers can identify subsets of major classes of mood disorders that may be responsive to alterations in sleep and diet.

Learning Objectives

- The learner will be able to describe how inflammatory markers are associated with alterations in mood, sleep and appetite.
- The learner will be able to describe interventions that alter inflammatory markers in depression and insomnia.

INFLAMMATION IN BIPOLAR DISORDER: A DIETARY TREATMENT LINK

Erika Saunders, Penn State College of Medicine

Individual Abstract Background: Epidemiological, human clinical, and rodent studies have linked metabolism of the polyunsaturated fatty acids (PUFA) to bipolar disorder (BD). Recent post-mortem studies link upregulation of brain omega-6 PUFA arachidonic acid (AA) metabolism to inflammatory products that worsen bipolar disorder (BD). Preclinical studies in rats indicated that mood stabilizers effective in BD downregulate brain AA metabolism. Methods: We report an observational, parallel group study designed to compare PUFA biomarkers between symptomatic BD subjects (N=30) before treatment and after symptomatic recovery, and healthy controls (HC; N=31). After a period of naturalistic follow-up, participants were either in remission or mildly depressed (N=15). Nine fatty acids were tested in esterified (E) and unesterified (U) forms. Ratios of U to E were calculated, as were ratios of DHA to ALA, EPA to ALA and EPA to DHA. Comparisons between groups were made with Student t-tests, paired t-tests, and chi-square tests. Pearson's r was used for bivariate correlations, and linear regression was used for multivariable analysis. Results: At baseline, plasma EPA levels were lower in BD than HC ($p=0.002$). At the follow-up time point in the BD group, levels of EPA increased and were comparable to the HC group. At follow-up, UDHA:ALA decreased ($p=4x10-5$) and UEPA:ALA decreased ($p=0.002$). EPA was negatively correlated with current panic attacks ($\beta=-0.37$, $p=0.04$), when corrected for age and sex. No fatty acids were correlated with depression or manic symptoms, or with use of medication by class. Reports of polyunsaturated fatty acid intake from the Food Frequency Questionnaire did not differ between groups at baseline or from baseline to follow-up in BD group, nor did they correlate with plasma levels of ALA, DHA or EPA. Conclusions: Differences in plasma EPA levels at baseline and at follow-up suggest that alterations of the fatty acid metabolism system may occur with treatment of BD. Studies of dietary supplements have shown mixed results. A different approach may lie in changing dietary intake of PUFA. Intriguing biological parallels exist with migraine headache, which overlaps with BD in clinical co-morbidity, epidemiology and treatment. Overlap in pathophysiology and treatments in BD and migraine suggests that dietary interventions involving PUFAs may be useful for both disorders. Indeed, a 12-week randomized trial comparing effects of a high EPA + DHA plus low omega-6 (H3-L6) dietary intervention to an intervention that only lowered omega-6 PUFA in 67 patients with chronic headaches showed clinical improvement in both groups, but the H3-L6 group experienced significantly greater reduction in headaches, quality-of-life and psychological distress. Based on the clinical and neuroinflammatory link between BD and migraine, we will outline a funded protocol to test if H3-L6 dietary intervention would be effective as an adjunct treatment of bipolar disorder.

Learning Objectives

- The learner will be able to describe findings of altered fatty acids in bipolar disorder.
- The learner will be able to describe the rationale for using dietary treatment interventions for bipolar disorder.

Literature References

- Rapoport SI. Lithium and the other mood stabilizers effective in bipolar disorder target the rat brain arachidonic acid cascade. ACS chemical neuroscience. 2014.
- Ramsden CE, Faurot KR, Zamora D, Suchindran CM, Macintosh BA, Gaylord S, Ringel A, Hibbeln JR, Feldstein AE, Mori TA, Barden A, Lynch C, Coble R, Mas E, Palsson O, Barrow DA, Mann JD. Targeted alteration of dietary n-3 and n-6 fatty acids for the treatment of chronic headaches: a randomized trial. Pain. 2013;154:2441-2451.

INFLUENCE OF DEPRESSIVE SYMPTOMATOLOGY AND TNFALPHA ON WEIGHT REGAIN

Paul Burghardt, Wayne State University

Individual Abstract Recidivism following weight loss is a major obstacle in obesity management. The risk of weight regain is impacted by psychological and physiological processes that are not completely understood. Fifty obese patients were enrolled in the Investigational Weight Management Clinic at the University of Michigan and followed a very low calorie diet (VLCD) intervention with a target weight loss of 15% of their baseline body weight. Cytokine profiles were measured using a custom luminex platform and depressive symptomatology was assessed using the Inventory of Depressive Symptomatology Self-Report (IDS-SR) before and after weight loss. Multiple regression analysis indicated that, after controlling for age, greater depressive symptomatology following weight loss predicted greater weight regain at 1-year post intervention (E.S. = 0.112, 95%CI [0.026, 0.198]). Levels of the inflammatory cytokine tumor necrosis factor alpha (TNF-alpha) after weight loss predicted lower weight regain at 1-year (E.S. = -0.516, 95%CI [-0.764, -0.267]), where those individual with higher TNF-alpha following weight loss showed lower weight regain. When exploring the potential influence of sex on these relationships, a more robust association between TNF-alpha and lower weight regain was found in men ($r= -0.549$, $p=0.003$; $n=28$) than women ($r= -0.259$, $p=0.204$; $n=22$). Further, a stronger positive association between depressive symptomatology and weight regain trended towards significance in women ($r=0.369$, $p=0.075$) but not men ($r=0.168$, $p=0.403$). The potentially protective effect of TNF-alpha in this specific instance may mediated by severity of depression and sex. The psychoimmunological state could be an important consideration that helps inform course of treatment in individuals with co-morbid depression and metabolic dysfunction.

Learning Objectives

- The learner will be able to describe the relationships between inflammatory markers and mood with risk of weight regain.
- The learner will be able to describe the potential impact of sex on inflammatory markers and the implications for weight regain.

Literature References

- Elfhag, K. and Rössner, S., (2005). Who succeeds in maintaining weight loss? A conceptual review of factors associated with weight loss maintenance and weight regain. obesity reviews. 6 (e.g. 2), pp.67-85
- Zahorska-Markiewicz, B.; Janowska, J. ; Olszanecka-Glinianowicz, M. ; Zurakowski, A., (2000). Serum concentrations of TNF-alpha and soluble TNF-alpha receptors in obesity. International Journal of Obesity. 24 (11), pp.1392-1395

PHENOTYPING INSOMNIA: THE STRESS AND IMMUNE INTERACTION AND ITS CLINICAL IMPLICATIONS

Julio Fernandez-Mendoza, Penn State Milton S. Hershey Medical Center

Individual Abstract Hyperactivity of the stress system is found in insomnia patients, while pro-inflammatory cytokines mediate daytime sleepiness and fatigue. Sleep/arousal biomarkers identify a phenotype of insomnia patients with objective short sleep duration who are at increased risk of cardiometabolic, neurocognitive, and psychiatric morbidity independent of behavioral factors. Findings from a longitudinal cohort of young children followed-up as adolescents and young adults (N = 421) showed that this insomnia phenotype is associated with increased cortisol levels (1.38 ± 0.08 μg/dL, $p = 0.007$) and pro-inflammatory cytokines (1.50 ± 0.16 pg/dL, $p = 0.025$) as compared to controls (1.13 ± 0.04 μg/dL and 1.11 ± 0.07 pg/dL, respectively). Data from a pilot clinical trial showed that a sedative antidepressant (SAD) decreases cortisol levels in middle-aged patients with insomnia, whereas cognitive-behavioral treatment (CBT) did not (ΔCortisol = -12.8 ng/mo vs. ΔCortisol = -0.7 ng/mo for SAD vs. CBT, respectively). Hypercortisolemia and hypercytokinemia not only mediate daytime fatigue in

insomnia with short sleep duration but also its increased risk of medical and psychiatric morbidity. New pharmacologic agents should target the underlying mechanisms of this more biologically severe insomnia phenotype.

Learning Objectives

- Increased cortisol and pro-inflammatory cytokines levels are associated with insomnia with objective short sleep duration.
- This insomnia phenotype may respond better to pharmacological vs. behavioral treatments.

Literature References

- Fernandez-Mendoza J, Vgontzas AN, Calhoun SL, Vgontzas A, Tsaoussoglou M, Gaines J, Liao D, Chrousos GP, Bixler EO: Insomnia symptoms, objective sleep duration and hypothalamic-pituitary-adrenal activity in children. Eur J Clin Invest 2014; 44:493-500.
- Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO: Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. Sleep Med Rev 2013; 1:241-254.

INFLAMMATION AS A PREDICTIVE BIOMAKERS OF RESPOSNE TO N-3 FATTY ACIDS IN MDD: A PROOF OF CONCEPT STUDY

Mark Rapaport, Emory University School of Medicine

Individual Abstract This study explores whether inflammatory biomarkers act as moderators of clinical response to omega-3 (n-3) fatty acids in subjects with Major Depressive Disorder (MDD). 155 subjects with DSM-IV MDD, a baseline 17-item Hamilton Depression Rating Scale (HAM-D-17) score ≥ 15 and baseline biomarker data (IL-1ra, IL-6, hs-CRP, leptin, adiponectin), were randomized between 05/18/06 and 06/30/11, to 8 weeks of double-blind treatment with eicosapentaenoic acid (EPA)-enriched n-3 1060 mg/day, docosahexaenoic acid (DHA)-enriched n-3 900 mg/day, or placebo. Outcomes were determined using mixed model repeated measures (MMRM) analysis for "high" and "low" inflammation groups based on individual and combined biomarkers. Results are presented in terms of standardized treatment effect size (ES) for change in HAM-D-17 from baseline to treatment week 8. While overall treatment group differences were negligible (ES=-0.13 to +0.04), subjects with any "high" inflammation improved more on EPA than placebo (ES=-0.39) or DHA (ES=-0.60) and less on DHA than placebo (ES=+0.21); furthermore, EPA-placebo separation increased with increasing numbers of markers of high inflammation. Subjects randomized to EPA with "high" IL-1ra or hs-CRP or low adiponectin ("high" inflammation) had medium ES decreases in HAM-D-17 scores versus subjects "low" on these biomarkers. Subjects with "high" hs-CRP, IL-6 or leptin were less placebo-responsive than subjects with low levels of these biomarkers (medium to large ES differences). Employing multiple markers of inflammation facilitated identification of a more homogeneous cohort of subjects with MDD responding to EPA versus placebo in our cohort. Studies are needed to replicate and extend this proof of concept work.

Learning Objectives The audience will learn about:

- The complexities involved in employing plasma markers of inflammation as biomarkers for studies of MDD;
- One approach for classifying patients with MDD based on inflammatory biomarkers.

Literature References

- Schmidt, H. D., Shelton, R. C. & Duman, R. S. Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. Neuropsychopharmacology 36, 2375-2394, doi:10.1038/npp.2011.151 (2011).
- McNamara, R. K. & Lotrich, F. E. Elevated immune-inflammatory signaling in mood disorders: a new therapeutic target? Expert Rev Neurother 12, 1143-1161, doi:10.1586/ern.12.98 (2012).
- Straub, R. H. Evolutionary medicine and chronic inflammatory state--known and new concepts in pathophysiology. J Mol Med (Berl) 90, 523-534, doi:10.1007/s00109-012-0861-8 (2012).

REPURPOSING DRUGS: A NEW LOOK AT THE PATHOPHYSIOLOGY AND THERAPEUTIC MANAGEMENT OF PSYCHIATRIC DISORDERS

Danielle Macedo, Neuropharmacology Laboratory, Universidade Federal do Ceará

Overall Abstract Psychiatric disorders are responsible for enormous emotional as well as financial burden on individuals, their families and society. Most of the available treatments are only palliative and most patients remain with residual symptoms despite our current knowledge. As an example, we can cite the treatment of major depressive disorder, bipolar affective disorder and schizophrenia. Additionally psychiatric patients present medical comorbidities such as heart and metabolic diseases. In recent years the strategy of repurposing drugs, that is, a drug used to treat one disease or condition being studied for the definition of its safety and effectiveness for treating other disease has gained increasing evidence. This is a crucial strategy to reduce the time frame, decrease costs and improve success rates since a new molecule takes more than 14 years to be translated to an approved drug. This is especially important for the management of psychiatric disorders mainly due to the recent findings related to its neurobiological alterations. Thus, to date, neuroinflammatory and oxidative alterations are important features related to these disorders. In line with this evidence drugs such as alpha-lipoic acid (ALA), carvedilol, candesartan and liraglutide are presenting neuroprotective properties and brain anti-inflammatory activity in diverse preclinical studies. Lipoid acid is used to treat diabetes neuropathic disease with potent antioxidant effects. Carvedilol is a nonselective alpha-1/beta blocker with antioxidant effects. Candesartana is an angiotensin 1 receptor blocker with anti-inflammatory properties. Liraglutide is a glucagon-like peptide-1 (GLP1) analogue used to treat diabetes. In this regard, our research group, at present, is devoting to the study of the effect of these drugs in animal models of psychiatric disorders. To date, we first described the antimanic [1] and antidepressant [2] effects of ALA. Recently, a manuscript showing the antimanic effect of carvedilol was accepted for publication in the periodic Neural Plasticity. Again a publication referring to antimanic effect of candesartan was submitted for publication. In this panel each of the four researchers will talk about their findings related to the effects of each drug, i.e. ALA (Prof. Silvania Vasconcelos), carvedilol (Prof. David de Lucena), candesartan (Prof. Danielle Macedo) and liraglutide (Prof. Clarissa Gama) in preclinical models of psychiatric disorders.

Learning Objectives

- Understanding of the importance of repurposing drugs in psychiatry;
- Acknowledgement of the antimanic and/or antidepressant effects of drugs such as carvedilol, candesartan and alpha-lipoic acid.

Literature References

- D. S. Macêdo, C. D. Medeiros, R. C. Cordeiro, F. C. Sousa, J. V Santos, T. a Morais, T. N. Hyphantis, R. S. McIntyre, J. Quevedo, and A. F. Carvalho, "Effects of alpha-lipoic acid in an animal model of mania induced by D-amphetamine.," Bipolar Disord., vol. 14, no. 7, pp. 707–18, Nov. 2012.
- M. C. C. Silva, C. N. S. de Sousa, L. R. L. Sampaio, N. C. Ximenes, P. V. P. Araújo, J. C. da Silva, S. L. de Oliveira, F. C. F. Sousa, D. S. Macêdo, and S. M. M. Vasconcelos, "Augmentation therapy with alpha-lipoic acid and des

CARVERDILOL AS ADJUVANTE DRUG IN BIPOLAR DISORDER TREATMENT

David De Lucena, Federal University of Ceará

Individual Abstract Bipolar disorder (BD) is a severe psychiatric disorder characterized by oscillation between periods of maniac and depressive episodes. The disease affects about 1 - 2% of the worldwide population causing great burden in patient's quality of life, generating high rates of functional disability. The pathophysiology of the disease remains unclear. The pathways hypothesized to take part of BD pathophysiology includes: dopamine deregulation, increased oxidative stress, decreased levels of neurotrophins and mitochondrial dysfunction among others. Based on the described above we investigated the effects of carvedilol, (CVD), a nonseletive beta-blocker widely used in the treatment of hypertension with antioxidant properties, in a model of mania induced by dimesilate of lisdexamfetamine (LDX) a prodrug metabolized to D-amphetamine, in rats. The experimental design of the study consisted of the evaluation of CVD against behavioral changes and oxidative stress alterations in two protocols of treatment, prevention and reversal using valproate (VAL) a mood stabilizer used as standard drug to assess the predictive validity of the model. In the prevention protocol the animals were pre-treated for 7 days with CVD, saline or VAL. In the reversal protocol the animals were pre-treated for 7 days with LDX and for further 7 days received CVD, saline or VAL plus LDX. The behavioral determinations of locomotor activity and social interaction were conducted 2 h after the last administration of LDX. Reduced glutathione (GSH) and lipid peroxidation (TBARS) levels were determined in brain areas of the prefrontal cortex (PFC) and striatum (EC) and brain-derived neurotrophic factor (BDNF) in the hippocampus (HC) rats. The results indicated that CVD prevented and reversed the hyperlocomotion and deficit in social contacts induced by LDX. In the neurochemical determinations CVD significantly prevented and reversed the alterations in BDNF, GSH and MDA levels induced by LDX presenting results comparable to those of saline and VAL groups. Therefore, the results of the present study indicates that CVD prevents and reverts the behavioral and neurochemical alterations induced by LDX used as an animal model of mania being, thus, a potential drug for the treatment of BD. These results were recently accepted for publication.

Learning Objectives

- The prevention and reversal effects of carvedilol in a pre-clinical animal model of mania.
- Antioxidant and neurotrophic mechanisms were associated with this effect.

Literature References

- "PRECLINICAL EVIDENCES FOR AN ANTIMANIC EFFECT OF CARVEDILOL," by Greicy Souza, Julia Gomes, Ana Isabelle Queiroz, Maíra de Araújo, Lígia Cavalcante, Michel Machado, Aline Monte, David de Lucena, João Quevedo, Andre Carvalho and Danielle Silveira Macêdo. Neural Plasticity. In press.
- Administration of carvedilol to mitigate tardive movement disorders, psychosis, mania, and depression; CM Swartz - US Patent 6,365,618, 2002 - Google Patents
- Noradrenaline transmission reducing drugs may protect against a broad range of diseases. P. J. Fitzgerald Article first published online: 1 OCT 2014 DOI: 10.1111/aap.12019

ANTIPSYCHOTIC AND ANTIDEPRESSANT EFFECTS OF TETRACYCLINES

Aline Monte, Federal University of Ceara

Individual Abstract Schizophrenia is a severe, chronic and debilitating mental disorder characterized by positive (e.g. hallucinations), negative (e.g. blunted affect and social isolation), and cognitive symptoms (e.g. executive and memory dysfunction). Although first-generation antipsychotics are effective in reducing positive symptoms, these agents have been relatively less effec¬tive in mitigating the severity of negative symptoms and cognitive deficits. In addition, drugs applied in the treatment of this brain disorder have the potential to cause extrapyramidal side effects by blocking D2 dopamine receptors generally located in the striatum. The relative absence of genuinely novel psychotropic agents, for most severe and persisting psychiatric disorders, is largely a consequence of the unavailability of sufficient disease models. In this context, a widely used animal model of schizophrenia involves the acute or repeated administration of ketamine, an antagonist to NMDA receptor that induces deficits in prepulse inhibition, memory and social interaction, which models the positive, cognitive and negative symptoms of schizophrenia. Increasing evidence points out that minocycline, a semi-synthetic second-generation tetracycline, has neuroprotective effects in different neurological conditions. The protective effects of this substance reside in its anti-inflammatory, neurotrophic, antioxidant, direct radical-scavenging and anti-apoptotic properties. Minocycline has been utilized successfully in some clinical trials since as an adjunctive therapy to antipsychotics for schizophrenia. Moreover, patients with schizophrenia showed that minocycline could improve their negative symptoms and/or cognitive functions. Taken together, the pharmacological and therapeutic profile of minocycline suggests that it may have clinical application in schizophrenia with the possibility of not only mitigating psycho¬pathology, but also modifying hypothesized disease processes. Our study investigated the effects of minocycline in the prevention and reversal of ketamine-induced schizophrenia-like behaviors in mice as well as some mechanisms underlying its effects. In the reversal protocol, animals received ketamine (20 mg/kg per day intraperitoneally or saline for 14 days, and minocycline (25 or 50 mg/kg daily), risperidone or vehicle treatment from days 8 to 14. In the prevention protocol, mice were pretreated with minocycline, risperidone or vehicle prior to ketamine. Behaviors related to positive (locomotor activity and prepulse inhibition of startle), negative (social interaction) and cognitive (Y maze) symptoms of schizophrenia were also assessed. Glutathione (GSH), thiobarbituric acid-reactive substances (TBARS) and nitrite levels were measured in the prefrontal cortex, hippocampus and striatum. Minocycline and risperidone prevented and reversed ketamine-induced alterations in behavioral paradigms, oxidative markers (i.e. ketamine-induced decrease and increase in GSH levels and TBARS content, respectively) as well as nitrite levels in the striatum. These data provide a rationale for evaluating minocycline as a novel psychotropic agent and suggest that its mechanism of action includes antioxidant and nitrergic systems, corroborating with the majority of the studies that reported a significant oxidative imbalance in schizophrenia. Our research group also studied, in a preclinical approach, the antidepressant effects of doxycycline. Similarly to minocycline doxycycline displays neuroprotective effects presenting a pharmacokinetics profile different from minocycline. Our study showed that doxycycline prevented and reversed the alterations induced by lipopolysaccharide (LPS), a neuroinflammatory model of depression. Like schizophrenia, the mechanisms underlying depression includes inflammation, oxidative and nitrosative stresses and neurotrophic alterations.

Anti-inflammatory, antioxidant and neurotrophic mechanisms were involved in the antidepressant-like effect of doxycycline. In conclusion tetracyclines seems to be important drugs for the management of psychiatric disorders, such as schizophrenia and depression.

Learning Objectives

- Describe the importance of inflammatory and oxidative mechanisms in schizophrenia and depression.
- Show that anti-inflammatory, antioxidant and neurotrophic mechanisms underlies tetracyclines antidepressant and antipsychotic actions.

Literature References

- Monte AS, de Souza GC, McIntyre RS, Soczynska JK, dos Santos JV, Cordeiro RC, Ribeiro BM, de Lucena DF, Vasconcelos SM, de Sousa FC, Carvalho AF, Macêdo DS. Prevention and reversal of ketamine-induced schizophrenia related behavior by minocycline in mice: Possible involvement of antioxidant and nitrergic pathways. J Psychopharmacol. 2013 Nov;27(11):1032-43.
- Chaves C, Marque CR, Maia-de-Oliveira JP, Wichert-Ana L, Ferrari TB, Santos AC, Araújo D, Machado-de-Sousa JP, Bressan RA, Elkis H, Crippa JA, Guimarães FS, Zuardi AW, Baker GB, Dursun SM1, Hallak JE. Effects of minocycline add-on treatment on brain morphometry and cerebral perfusion in recent-onset schizophrenia. Schizophr Res. 2014 Dec 11 [In press].
- Mello BS, Monte AS, McIntyre RS, Soczynska JK, Custódio CS, Cordeiro RC, Chaves JH, Vasconcelos SM, Nobre HV Jr, Florenço de Sousa FC, Hyphantis TN, Carvalho AF, Macêdo DS. Effects of doxycycline on depressive-like behavior in mice after lipopolysaccharide (LPS) administration. J Psychiatr Res. 2013, 47(10):1521-9.

BIPOLAR DEPRESSION AND NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: TARGETING GLUTAMATE AND ITS ROLE ON NEUROINFLAMATION

Clarissa Gama, UFRGS, HCPA, Porto Alegre, Brazil

Individual Abstract The neurobiology of mental disorders involves alterations in glutamatergic neurotransmission. These alterations are partially triggered by pro-inflammatory cytokines, cortisol and oxidative stress that are known to increase the activity of the enzyme indoleamine 2,3-Dioxygenase (IDO) responsible for the metabolization of tryptophan. In this pathway kynurenic acid and quinolinic acid are formed. Kynurenic acid is an NMDA receptor antagonist whereas quinolinic acid is a NMDA agonist. Recent evidences point towards an increase in kynurenic acid levels in schizophrenia while in depression an increase in quinolinic acid is mainly observed. Due to the relationship among oxidative stress, neuroinflammation and glutamatergic neurotransmission I participated of clinical studies using the antioxidant compound N-acetylcysteine (NAC) as adjunctive treatment for bipolar depression. N-acetylcysteine is a glutamate modulator and glutathione precursor that effectively replenishes brain glutamate and glutathione levels being usually prescribed for chronic bronchitis, chronic obstructive pulmonary disease (COPD) among other lung diseases. In this randomized placebo controlled trial, 149 individuals with moderate depression during the 2 month were administered 1 g BID of NAC. The results showed that the estimated mean baseline Bipolar Depression Rating Scale (BDRS) score was 19.7 (SE = 0.8), and the mean BDRS score at the end of the 8 week open label treatment phase was 11.1 (SE = 0.8). This reduction was statistically significant ($p < 0.001$). Improvements in functioning and quality of life were similarly evident. In conclusion, these open label data demonstrate a robust decrement in depression scores with NAC treatment. We also conducted clinical studies using memantine, a drug approved by the FDA for the treatment of moderate to severe Alzheimer's disease, acting as weak non-selective NMDA receptor antagonist for improvement of schizophrenia negative and positive symptoms with amantadine as add-on therapy to antipsychotics. In this study amantadine, a memantine's derivate, was used as adjunctive therapy to the antipsychotic clozapine in four cases of DSM-IV schizophrenia. To our surprise, the improvement was not only in negative symptoms, and we have also found improvement in positive symptoms and cognition. Taken together, these clinical studies brings further evidence base supporting a key role of glutamate in the pathophysiology of bipolar depression and schizophrenia.

Learning Objectives

- To review the relationship among glutamatergic neurotramission, neuroinflammation and oxidative stress.
- Bring clinical evidences of the importance of glutamate-modulating drugs, as add-on therapy, for the management of schizophrenia and bipolar depression.

Literature References

- Berk M, Dean OM, Cotton SM, Gama CS, Kapczinski F, Fernandes B, Kohlmann K, Jeavons S, Hewitt K, Moss K, Allwang C, Schapkaitz I, Cobb H, Bush AI, Dodd S, Malhi GS. Maintenance N-acetyl cysteine treatment for bipolar disorder: a double-blind randomized placebo controlled trial. BMC Med. 2012 Aug 14;10:91
- Gama CS, Lucena DD, Cruz C, Lobato MI, Belmonte-de-Abreu PS. Improvement of schizophrenia negative and positive symptoms with amantadine as add-on therapy to antipsychotics: a case series. Rev Bras Psiquiatr. 2010, 32(2):193-4.

OPTIMIZING FIRST EPISODE SCHIZOPHRENIA MEDICATION TREATMENT BY COMMUNITY CLINICIANS: THE RAISE-ETP MODEL

Delbert Robinson, Hofstra NS-LIJ School of Medicine

Overall Abstract The recommended antipsychotic medication treatment for first episode schizophrenia differs from that for multi-episode schizophrenia, e.g. the suggested sequence of medications to try differ and optimal dose for the first episode is around half of the dose for multi-episode patients with many agents. Since the experience of most community care clinicians is heavily weighted towards the treatment of multi-episode patients, communicating specialized knowledge about first episode treatment to busy clinicians is a challenge. This symposium will present the model developed for The RAISE-ETP study. RAISE-ETP was a cluster-randomized clinical trial that compared NAVIGATE, an integrated team-based treatment program that included medication treatment for first episode schizophrenia-spectrum disorders, with community care at 34 clinics in 21 US states. Four hundred four subjects were included in the trial. Dr. Robinson will present the RAISE- ETP medication sequences and an overview of COMPASS, a web-based computer patient prescriber communication tool and decision support system developed for RAISE-ETP and implemented as part of NAVIGATE. Dr. Achytes will present data on patient and prescriber use of COMPASS and also the perspective of community clinicians using decision support systems. Dr. Schooler will report data comparing medication and side effect outcomes between subjects treated using COMPASS compared to those subjects treated with usual community care practice.

Learning Objectives

- At the end of the session, attendees will be able to describe the differences between recommended medication treatment for first episode and multi-episode schizophrenia.

- At the end of the session, the listener will be able to describe the advantages and limitations of computer decision support systems. Regarding specific RAISE-ETP outcomes, attendees will be able to describe differences and similarities between COMPASS and community treated subjects in medication use and self-reported side effects.

DEVELOPING MEDICATION STRATEGIES FOR THE RAISE-ETP STUDY

Delbert Robinson, Hofstra NS-LIJ School of Medicine

Individual Abstract RAISE-ETP was mandated by NIMH to be performed at community facilities. To fulfill this requirement, we developed an integrated, team-based treatment program called NAVIGATE. Patient engagement and long-term retention in treatment is particularly important with young people starting treatment for psychosis. NAVIGATE employed a shared decision making framework for all treatments; this model was chosen (among other reasons) to maximize engagement and retention. For medication treatment, the strategy was to provide the broadest array of marketed medication options that were evidence-based to patients and prescribers for consideration and choice based upon individual preferences. Randomized comparison trials have not demonstrated efficacy differences between antipsychotics for treatment of first episode patients but have highlighted the importance of low dose strategies and the high rates of side effects despite using low doses. Given the importance of dosing and side effect profiles with first episode treatment, suggested NAVIGATE antipsychotic medication treatment focused upon using agents that had been studied with first episode patients or adolescent populations. A panel of experts reviewed the first episode treatment literature and classified antipsychotic medications into groups for use at different treatment stages based primarily upon side effect profiles (the exception being clozapine for subjects who did not improve with other antipsychotics). As most community clinicians' treatment experience is heavily weighted towards treatment of multi-episode patients, we developed COMPASS, a decision support system using measurement based care accessed by clinicians via web browsers from a secure server, to convey specialized first episode treatment information to busy clinicians. COMPASS includes patient self report of symptoms, adherence, side effects and substance use. These data provide a means for patient concerns to be communicated to prescribers. Further, the prescriber interview is modified in real time by the patient self report. Details of the medication algorithm and of COMPASS will be presented at the meeting.

Learning Objectives

- At the end of the session, attendees will be able to describe the differences between recommended medication treatment for first episode and multi-episode schizophrenia.
- At the end of the session, the listener will be able to describe the COMPASS decision support system developed for the RAISE-ETP study.

Literature References

- Robinson DG, Schooler NR, John M, Correll C, Marcy P, Addington J, Brunette MF, Estroff SE, Mueser KT, Penn D, Robinson J, Rosenheck RA, Severe J, Goldstein A, Azrin S, Heinssen R, Kane JM. Medication Prescription Practices for the Treatment of First Episode Schizophrenia-Spectrum Disorders: Data from the National RAISE-ETP Study. Am Journal Psychiatry, in press.
- Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, Himelhoch S, Fang B, Peterson E, Aquino PR, Keller W: The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull 2010;36(1):71–93

USE OF A PATIENT-PRESCRIBER COMPUTERIZED COMMUNICATION AND DECISION SUPPORT TOOL IN RAISE-ETP: THE COMPASS SYSTEM

Eric Achtyes, Michigan State University College of Human Medicine

Individual Abstract Physician adherence to published treatment guidelines is often low across many specialties in medicine, including psychiatry. In the RAISE-ETP study a computerized decision support tool (COMPASS) was developed to assist prescribers in utilizing evidence-based approaches for the treatment of the specialized subpopulation of first-episode psychosis patients. This tool was used by prescribers (psychiatrists and nurse practitioners) and patients in 17 community mental health settings in the NIMH-sponsored RAISE-ETP study. A COMPASS medication visit began with obtaining vital signs and patients completing self-reported ratings of symptoms, side effects, adherence and substance use. These results were entered directly into a computer system using a web-based interface. The patient self report ratings were then used to inform the prescriber during the interview with the patient. The prescriber entered a complimentary assessment into the COMPASS system, which then provided immediate decision support. Patients completed a total of 3939 COMPASS-guided visits with prescribers. Analyses of the patterns of patient responses were consistent with patient improvement over time, e.g. patients were significantly less likely to report the presence of symptoms such as depressed mood or a wish to make a change in their medications. Details of these analyses and of prescriber use and experiences with the COMPASS decision support system for first-episode psychosis treatment will be presented.

Learning Objectives

- At the end of the presentation, participants will understand the advantages and challenges of using computerized decision support systems for the treatment of first-episode psychosis patients.
- At the end of the presentation, participants will appreciate the end-user experience of implementing computerized decision support systems during prescriber visits with patients with first-episode psychosis.

Literature References

- Miller AL, Crismon ML, Rush AJ, Chiles J, Kashner TM, Toprac M, Carmody T, Biggs M, Shores-Wilson K, Chiles J, Witte B, Bow-Thomas C, Velligan DI, Trivedi M, Suppes S, Shon, S: The Texas Medication Algorithm Project. Schizophr Bull 2004; 30:627-647
- Trivedi MH, Kern JK, Baker SM, Altshuler KZ. Computerizing medication algorithms and decision support systems for major psychiatric disorders. J Psychiatr Pract 2000; 6:237-246

MEDICATION CHOICES, VITAL SIGNS AND SELF REPORTED SIDE EFFECTS IN THE RAISE-ETP RCT: COMPARING NAVIGATE, AN INTEGRATED TEAM BASED TREATMENT PROGRAM, TO COMMUNITY CARE

Nina Schooler, SUNY Downstate Medical Center

Individual Abstract The RAISE-ETP study used cluster randomization to compare NAVIGATE, an integrated team-based treatment program to Community Care for first episode psychosis at 34 sites in the US. Seventeen sites were randomly allocated to provide NAVIGATE and 17 provided Community Care, all treatments customarily available at the site. NAVIGATE included an individual strength based psychological therapy, family psychoeducation and supported employment education as well as a web accessible decision support system for prescribers and patients called COMPASS. Treatment and follow-up continued for at least 24 months following enrollment. The trial was conducted between July 2010 and July 2014. All subjects participated in a common assessment battery. This presentation will focus on data drawn from the battery that are especially relevant to medication use. These include vital signs and BMI assessed at baseline, 3, 6, 12, 18 and 24 months, and self reported medication prescriptions and side effects completed monthly during the 24 months of the study. Two hundred twenty three subjects were enrolled at the NAVIGATE sites and 181 at Community Care sites. Subject characteristics for NAVIGATE and Community Care were: average age (23.1/23.2); gender (male 66.3%/77.6%) race (white 44.2%/61.9%); education (completed high school 32.0%/33.6%); diagnosis (schizophrenia 55.8%/50.7%); median duration of untreated psychosis in weeks (66/88); (ever hospitalized (81.2%; 75.8%). The presentation will compare self reported medication use that includes specific antipsychotic medications and dose prescribed, self reported side effects and vital signs, including BMI. We test the hypothesis that decision support for prescribers results in: choice of antipsychotic medications according to expert recommendations; low dose of medications used; improved health outcomes as measured by vital signs and BMI and reduced side effects related to antipsychotic medications. The importance of these outcomes is highlighted by the report that 48.7% of subjects in the RAISE-ETP study were overweight or obese at baseline 1 and the finding that BMI increased significantly more in Community Care compared to NAVIGATE over the 24-month study period.

Learning Objectives

- Attendees will be able to describe differences and similarities between COMPASS and community treated subjects in the antipsychotic medications used and the degree to which they agree with guidelines for first episode psychosis patients.
- Attendees with be able to describes differences and similarities between COMPASS and community treated subjects in self-reported side effects, vital signs and BMI.

Literature References

- Correll CU, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck R, Marcy P, Addington J, Estroff SE, Robinson J, Penn D, Azrin S, Goldstein A, Severe JB, Heinssen R, Kane JM. Cardiometabolic Risk in First Episode Schizophrenia-Spectrum Disorder Patients: Baseline Results from the Recovery After an Initial Schizophrenia Episode Early Treatment Program (RAISE-ETP) Study JAMA Psychiatry 2014 10 on line pub doi:10.1001/jamapsychiatry.2014.1314
- Robinson DG, Schooler NR, Correll CU, Marcy P, Addington J, Brunette MF, Estroff SE, Mueser KT, Penn D, Robinson J, Rosenheck R, Severe J, Goldstein A, Azrin A, Heinnsen R, Kane JM Medication Prescription Practices for the Treatment of First Episode Schizophrenia-Spectrum Disorders: Data from the National RAISE-ETP Study. Am J Psychiatry 2014 08 In Press

3:30 p.m. - 4:30 p.m.
Individual Research Reports

A HUMAN LABORATORY STUDY OF BACLOFEN'S BIOBEHAVIORAL MECHANISMS IN AFFECTING ALCOHOL CONSUMPTION

Mehdi Farokhnia, Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, Laboratory of Clinical and Translational Studies, National Institute on Alcohol Abuse and Alcoholism and Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health

Steven Edwards, William Zywiak, John McGeary, Robert Swift, George Kenna, Lorenzo Leggio

Abstract BACKGROUND: Baclofen, a selective GABA-B receptor agonist, has been identified as a promising pharmacological treatment for alcohol use disorder. In preclinical studies, baclofen has been shown to suppress acquisition and maintenance of alcohol-drinking behavior, oral self-administration and motivational properties of alcohol, and the severity of the alcohol withdrawal syndrome. Similarly, human studies indicate that treatment with baclofen reduces alcohol drinking and craving and promotes abstinence in alcohol dependent individuals. By contrast, another trial in alcoholics with a low severity of dependence found a robust treatment effect, but no differences between baclofen and placebo. The few treatment studies available lead one to conclude that baclofen represents a promising medication in the treatment of alcohol dependence but deserves further investigation. In particular, the biobehavioral mechanisms by which baclofen reduces drinking are not well characterized. The aim of this study was to investigate baclofen's impact on alcohol drinking and its possible biobehavioral mechanisms in a clinical laboratory paradigm.

METHODS: This was a between-subject, double-blind, placebo-controlled, randomized human laboratory study. Fourteen non-treatment seeking, alcohol-dependent (DSM-IV diagnosis), heavy drinking (≥4 and ≥5 drinks/day for women and men, respectively) outpatients were randomized to receive either baclofen (30 mg/day) or placebo for 7 days. At day 8, each participant performed an alcohol cue-reactivity (CR) followed by an alcohol self-administration (ASA) in a private bar-like testing room. CR: Participants were exposed to visual, tactile, olfactory, and proprioceptive stimuli associated with the beverage (water or alcohol) during three consecutive CR trials. At the end of each trial, patients rated their urge and attention to alcohol using the Alcohol Urge Questionnaire (AUQ), and the Alcohol Attention Scale (AAS). Mean Arterial Pressure (MAP) and Heart rate (HR) were continuously monitored and the amount of salivation was measured using three dental rolls placed in the participants' mouths. ASA: A priming drink was first presented and participants were instructed to consume it within 5 minutes. Forty minutes after that, additional alcohol was presented in a form of 2 trays with 4 mini-drinks each. Participants were allowed to drink any or all glasses and $3 per drink was provided as an alternative reinforcer for not drinking. Alcohol's stimulant and sedative effects were assessed using the Biphasic Alcohol Effects Scale (BAES) every 10 minutes after the priming and every 30 during the alcohol free choice period.

RESULTS: During the CR session, there were no significant differences between the two groups in terms of urge (AUQ) and attention (AAS) to alcohol. Repeated measures ANCOVA demonstrated a significantly higher MAP for the baclofen group compared to the placebo group [$F(1,25)=5.36$, $p=0.03$], but the HR readings were not significantly different. Baclofen, compared with placebo, significantly increased salivation [$F(1,24.4)=15.97$, $p<0.01$]. During the ASA, baclofen-treated patients consumed a lower amount of alcohol than the placebo group (0.17 ± 0.41 vs. 1.43 ± 2.30 standard drinking units, $t(6.4)=1.43$, $p=0.20$). Although this difference was not statistically significant, there was a robust medication effect ($d=0.76$). When drinking during the ASA plus two days before were combined in the analysis, there was a significant effect of baclofen to reduce alcohol consumption [$F(1,35.69)=10.98$, $p<0.01$]. After consuming the priming drink, there was a significant effect of baclofen, compared to placebo, on the biphasic effects of alcohol; Repeated measures ANCOVA showed significant medication

effect on BAES stimulation [F(1,92.5)=11.30, p=0.001, mean difference=1.67 (SE=0.50)] and BAES sedation [F(1,90)=9.99, p<0.01; mean difference=1.10 (SE=0.35)].
CONCLUSION: Baclofen was shown to reduce alcohol consumption during both the naturalistic phase and the ASA. The present study suggests that baclofen's impact on the biphasic effects of alcohol (stimulation and sedation) might be its main biobehavioral mechanism of action in reducing alcohol drinking. In fact, the effects of baclofen on alcohol's sedation may exert an aversive effect on the subjective experiences of alcohol consumption, reducing individuals' motivation to drink more alcohol, as we observed during the ASA. While participants reported an increase in sedation in the BAES, no clinically significant sedative side-effects (sedation, tiredness, sleepiness) were reported while participants took the medication, confirming the already reported safety of baclofen in alcohol dependent patients. In this study we did not find an effect of baclofen in reducing alcohol craving nor in the attention to alcohol cues during the CR. The results of this study should be interpreted in light of its strengths and limitations. The most important limitation was the small sample, which raises the issue of possible type II errors. As such, the overall goal of this study was to provide preliminary findings that may guide future larger trials. Furthermore, baclofen was only tested at the 30 mg/day dose in this trial. Future controlled studies should assess baclofen's efficacy at different doses in treatment and human laboratory studies (even with different doses of alcohol administered). This is the first human laboratory alcohol study testing baclofen in AD individuals, after having taken baclofen for a reasonable period of time before performing laboratory procedures. Moreover, this is one of the first studies combining CR and ASA, thus providing a more comprehensive assessment of biobehavioral mechanisms of the drug. Our team is currently performing a follow-up larger study using a similar design but targeting specifically alcohol-dependent individuals with high anxiety levels.

Learning Objectives

- Given the high prevalence of alcohol use and associated health problems, it's essential to explore and develop new pharmacological options to treat alcohol use disorder.
- In this study, baclofen could reduce alcohol consumption in alcohol dependent individuals, an effect that seems to be mediated through baclofen's impact on the biphasic effects of alcohol as its main biobehavioral mechanism of action.

Literature References

- Flannery BA, Garbutt JC, Cody MW, Renn W, Grace K, Osborne M, Crosby K, Morreale M, Trivette A: Baclofen for alcohol dependence: a preliminary open-label study. Alcohol Clin Exp Res 2004; 28(10):1517-1523
- Addolorato G, Leggio L, Agabio R, Colombo G, Gasbarrini G: Baclofen: a new drug for the treatment of alcohol dependence. Int J Clin Pract 2006; 60(8):1003-1008

ATROPHY PATTERNS IN ALZHEIMER'S DISEASE EXHIBIT NETWORK PROPERTIES

Ram Bishnoi, UTHSCSA
Peter Fox, Donald Royall

Abstract Background: The ongoing quest to delineate the brain network architecture (aka, "the connectome") with ever-improving accuracy, resolution and complexity embraces the integration of brain imaging modalities. Functional magnetic resonance imaging (fMRI), using both task-control contrasts and resting-state (rs-fMRI) is widely used to identify functional connectivity networks (FCNs). Diffusion tensor imaging (DTI), a structural MRI method, also is used extensively to chart the white-matter tracts connecting grey-matter regions. More recently, regional grey-matter volumes (GMV) among functionally and/or tractographically connected networks have been demonstrated to co-vary both during development (rising GMVs) and in neurodegenerative disorders (falling GMVs). GMV patterns can be conceptualized and analyzed in terms of structural covariance networks (SCNs). In Alzheimer's disease (AD) atrophy is observed chiefly in brain regions implicated in the default mode network (DMN), a network typically defined by rs-fMRI FCN patterns. In keeping with this DMN specificity, decreased connectivity in the DMN has been repeatedly reported in AD. A more recent observation is that decreased SCN connectivity can also be observed in the DMN in AD. Here, we apply structural equation modeling (SEM) to delineate and quantify AD-specific alterations in SCNs using a novel meta-analytic method applied to voxel-based morophometry (VBM) studies in the BrainMap database (BrainMap.org). Prior meta-analyses have applied graph theoretical modeling (GTM) to the VBM sector of BrainMap, demonstrating convergent SCNs for multiple neurodegenerative disorders. Here, for the first time, we construct an AD-specific meta-analytic model using this resource.
Methods: From the BrainMap database, 62 non-redundant, whole-brain VBM experiments reporting regional atrophy in AD we extracted from 52 peer-reviewed manuscripts. These experiments included data from 2974 AD patients and 2509 matched controls. Novel modeling techniques were applied to construct an AD-specific SCN, as follows. 1st convergent regions of atrophy were identified through activation likelihood estimation method (ALE). 2nd regions of interests (ROIs) were selected around centers of ALE convergence. 3rd these ROIs were employed to identify covariance pattern in AD and co-activating regions in healthy controls to construct SCNs and FCNs respectively. 4th the derived SCN model was subjected to multivariate analysis (SEM) to take into account all regional interdependencies and to increase sensitivity. For SEM analyses, modeled atrophy scores were extracted from per-experiment modeled-atrophy (MA) maps using ROIs.
Results: The atrophy pattern of AD involved bilateral medial temporal lobes, bilateral inferior parietal lobules, posterior cingulate cortex and precuneus, thalamus and left middle temporal gyrus. These regions showed structural interdependence forming a network with one additional region, left prefrontal cortex which covaried with left inferior parietal lobule. The functional connectivity pattern of these regions was extensive (included anterior cingulate, medial prefrontal, and bilateral lateral prefrontal cortices), and overlapped the default mode network (DMN). SCN of AD, on the other hand was overlapped the "posterior" part of default mode network (DMN). Observed divergence was striking but to increase sensitivity of network model, the data-driven SCN network was used as a priori model in SEM. The goodness of fit was excellent (Chi square=1.515, p=0.824, CFA=1, RMSEA=0). To identify the best fitting model that can account for data, we employed algorithm for automatic identification of best fitting model. Bootstrapping the data generated a confidence interval (CI) for goodness-of-fit of the best model and our model's fits indices were found to be within CI.
Conclusion: We conclude that 1) the characteristic atrophy pattern in AD corresponds to its SCN, which overlaps with FCNs closely but not completely. 2) Network modeling techniques used in FCN analysis can be successfully employed to identify structural covariance. 3) Multivariate analyses of voxel-based morphometric data can enhance statistical power of proposed network model.

Learning Objectives

- To understand structural covariance, and identification structural covariance network intrinsic to Alzheimer's disease.
- To understand novel network modeling techniques and structural equation modeling in neuro-imaging network analysis.

Literature References

- Alexander-Bloch A, Giedd JN, Bullmore E. Imaging structural co-variancebetween human brain regions. Nat Rev Neurosci. 2013 May;14(5):322-36.

- Fox PT, Lancaster JL, Laird AR, et al. Meta-analysis in human neuroimaging: computational modeling of large-scale databases. Annu Rev Neurosci. 2014;37:409-34.

AFFECTIVE PROCESSING IN PEDIATRIC BIPOLAR DISORDER AND OFFSPRING OF BIPOLAR PARENTS

Isabelle Bauer, University of Texas at Houston
Thomas D. Frazier, Eric Youngstrom, Giovana B. Zunta-Soares, Jair C. Soares

Abstract Background: Bipolar disorder (BD) is characterized by biased processing of emotional information. However, little research in this area has been conducted in youth with BD and at- risk individuals.
Purpose: The goal of this study was to determine whether children with BD displayed comparable or more severe manifestations of this bias relative to offspring with BD.
Methodology: The sample (N=64 children and adolescents) included 18 individuals with BD (13.7±2.51 years, 8 males), 13 healthy BD offspring (11.56±3.18 years, 6 males), 10 BD offspring suffering from psychiatric disorders other than BD (11.34±2.97 years, 5 males), and 23 healthy controls (HC-12.78±3.08 years, 8 females). All participants performed the Affective Go/No-Go (AGN) and the Rapid Visual Processing (RVP) tasks of the Cambridge Neuropsychological Test Automated Battery (CANTAB).
Results: Relative to HC, individuals with BD responded faster to correct trials and committed an elevated number of commission errors across all affective conditions of the AGN task. By contrast, affected BD offspring showed intact performance accuracy but quicker response times than HC. Mean reaction times and total false alarmsnumber of errors in the RVP task were comparable across groups.
Discussion & future directions: In line with previous findings children with BD encountered difficulties in processing affective information. The tendency toward faster but accurate responses to affective stimuli observed in the affected offspring group may be a marker of increased efficiency in processing affective information. The current results yield potential implications for the development of early prevention and intervention strategies focusing on affective processing in youth with BD and at-risk individuals.

Learning Objectives

- Improve knowledge on affective processing in children and adolescents with bipolar disorder.
- Determine whether youth with bipolar disorder display comparable or more severe manifestations of affective bias relative to healthy bipolar disorder offspring, bipolar disorder offspring with psychiatric disorders other than bipolar disorder and healthy controls.

Literature References

- Gotlib IH, Traill SK, Montoya RL, Joormann J, Chang K. Attention and memory biases in the offspring of parents with bipolar disorder: indications from a pilot study. Journal of Child Psychology and Psychiatry. 2005;46(1):84-93.
- Passarotti AM, Sweeney JA, Pavuluri MN. Fronto-limbic dysfunction in mania pre-treatment and persistent amygdala over-activity post-treatment in pediatric bipolar disorder. Psychopharmacology (Berl). Aug 2011;216(4):485-499.

EXCLUSION CRITERIA IN PLACEBO CONTROLLED ANTIDEPRESSANT EFFICACY TRIALS: A REVIEW OF THE PAST 20 YEARS OF PUBLISHED RESEARCH

Mark Zimmerman, Brown University
Heather Clark

Abstract Introduction: Challenges to the generalizability of antidepressant efficacy trials (AETs) to patients treated in the real world have been raised for decades. More than a decade ago our clinical research group found that the vast majority of depressed patients presenting for treatment to our outpatient practice would have likely been excluded from in an AET because they did not meet the study's inclusion and exclusion criteria. Subsequent studies replicated our finding that most depressed outpatients treated in clinical practice would not qualify for an AET. Moreover, there was some evidence that treatment response differed between outpatients who would and would qualify for an AET. In the present report we conducted a comprehensive review of placebo-controlled AETs published over the past 20 years in order to determine whether there have been any changes in these criteria subsequent to the publications that highlighted the unrepresentativeness of the depressed patients studied in AETs. We identified 163 placebo-controlled AETs published during the past 20 years. We compared the inclusion/exclusion criteria of studies published during the past 5 years compared to the prior 15 years.
Methods: To ascertain the sample of studies of AETs we reviewed the tables of contents of 49 journals from January, 1995 through December, 2014. We also examined the reference lists of meta-analyses of AETs, and the studies identified from our literature review. We did not include trials that focused on refractory depression, chronic depression, bipolar, psychotic, atypical or melancholic subtypes of depression, trials focused on depressed patients with particular symptoms such as anxious features, trials based on inpatient samples, or trials limited to patients with a particular comorbid condition such as alcoholism, anxiety disorder, or medical illness. We only included trials focused on patients with major depression, and therefore did not include trials that were based on admixture of patients with major depression, dysthymic disorder, and minor depression. Trials resulting in multiple publications based on the same sample (and same set of inclusion/exclusion criteria) were included only once. We did not include trials of intravenous or injectable forms of medication, and also did not include trials of medication combination or augmentation strategies. We included trials whether or not the medication has received regulatory approval for the treatment of depression.
Two of the authors independently reviewed each article and completed a form listing the psychiatric inclusion and exclusion criteria used in the study. The reviewers met, compared the results of their data abstraction, and resolved discrepancies. We compared the inclusion/exclusion criteria of studies published during the past 5 years (2010-2014) compared to the prior 15 years (1995-2009).
Results: We identified 163 placebo-controlled AETs published during the past 20 years, 50 of which were published during the past 5 years. Recent studies were significantly more likely to exclude patients with comorbid Axis I disorders and personality disorders, exclude patients because the episode duration is too long or too short, and exclude patients who made a suicide attempt in the past. The severity threshold on depression rating scales required for inclusion is higher in the more recent studies.
Discussion: The results of this review suggest that in inclusion/exclusion criteria for AETs have narrowed over the past five years thereby suggesting that AETs are even less generalizable than they were previously (when concerns about their generalizability had already been raised).

Learning Objectives

- At the conclusion of this presentation, the participant should become familiar with the most commonly used inclusion/exclusion criteria in placebo-controlled studies of antidepressant medication over the past 20 years.
- At the conclusion of this presentation, the participant should become familiar with the changes in the inclusion/exclusion criteria used in placebo-controlled studies of antidepressant medication over the past 20 years.

Literature References

- Zimmerman, M., Mattia, J.I. & Posternak, M.A. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice. American Journal of Psychiatry, 2002, 159, 469-473.
- Zimmerman, M., Chelminski, I. & Posternak, M.A. Exclusion criteria used in antidepressant efficacy trials: Consistency across studies and representativeness of samples included. Journal of Nervous and Mental Disease, 2004, 192, 87-94.

ACETAZOLAMIDE: A NEW ADHERENCE MARKER FOR CLINICAL TRIALS

Aidan Hampson, National Institute of Health/NIDA
Sharon Walsh, Shanna Babalonis, Paul Nuzzo, Michelle Lofwall

Abstract Medication adherence is a key assumption in clinical trials. Unmonitored adherence failure can result in the inappropriate and expensive cessation of a drug's development. One currently used method to confirm medication consumption uses riboflavin as a marker compounded with the medication and assessed by urine analysis. However riboflavin is physiologically present, rapidly excreted and medication consumption can be masked or mimicked by consumption of multi-vitamins or energy drinks. This study examines the carbonic anhydrase inhibitor acetazolamide (ACZ) as a putative new adherence marker for clinical trials. An ultra-low dose (ULD, 15mg, 6% of minimum clinical dose) of ACZ was chosen because it is an easily detected, FDA approved drug that is not metabolized and exclusively eliminated in urine. Specifically this study examines the plasma, whole blood and urinary pharmacokinetics (PK) of ACZ in 10 normal human subjects. The study also examines the effect of ULD ACZ co-administration on the pharmacodynamics (PD) and PK of OxyCodone (30 mg/day p.o., Oxy), a model medication chosen because its PD is easily followed. Results: ULD ACZ dosing resulted in a mean plasma maximum concentration (Cmax) of 1358 ng/ml (SD 531), which occurred (Tmax) 1.1h (SD, 0.6) post administration. The elimination of ACZ from plasma showed two distinct phases, initial elimination proceeded with a half-life (T1/2) of 0.8h (SD 0.4), but after 4-6h and for the remainder of the 96h study period, elimination was dominated by a beta phase with a T1/2 of 19.9h (SD 3.4). In whole blood, PK was distinct from that in plasma, Cmax occurred at 4-6h, with an elimination T1/2 of 44.9h (SD 9.2). The key parameter for an adherence marker is urinary elimination rate, as this defines detection period. For ULD ACZ, 1 compartment analysis predicted a urinary elimination T1/2 of 16h (SD 2.7) or 29.5h (SD 6.1) for the beta phase of a 2 compartment analysis. In all matrices inter-subject variability was low and the PK of ACZ was unaffected by Oxy co-administration. The Cmax, Tmax and elimination T1/2 of co-administered Oxy was unaffected by ULD ACZ. The AUC of co-administered OXY was increased by 20% (SD 11.2), although this may be an artifact due to outliers in a small sample size. The PD of Oxy was unaffected by ULD ACZ in all of the subjective and physiological parameters recorded. Conclusions: ULD ACZ is long-lived, easily detected for an extended period and its urinary elimination rate showed remarkably little inter-subject variability. This is possibly due to its complete elimination in urine and lack of hepatic interaction, a feature that also reduces the risk of interaction with test medications. Compared with riboflavin which is detectable for around 24h post-dose, ULD ACZ exhibits the features of a significantly improved adherence marker, one that may extend assessment of "time since last dose" to a several day period.

Learning Objectives

- To exemplify the use of a new adherence marker for clinical trials.
- To describe the characteristics of Acetazolamide as a marker and so promote its use in clinical trials.

Literature References

- Czobor P, & Skolnick P: The Secrets of a Successful Clinical Trial: Compliance, Compliance, and Compliance. Molecular Interventions, (2011) 11(2), 107–110.
- Ritschel WA, Paulo C, Arancibia A, Agrawal MA, Wetzelsberger KM, Lucker PW: Pharmacokinetics of acetazolamide in healthy volunteers after short- and long-term exposure to high altitude. J Clin Pharmacol 1998: 38(6): 533-539.

MEASURING STATISTICALLY AND CLINICALLY MEANINGFUL CHANGE IN CLINICAL TRIALS: MOVING AWAY FROM PERCENT CHANGE AND ARBITRARY CHANGES IN SCORES

Anzalee Khan, ProPhase, LLC
Tim Victor, Mark Opler, Jonathan Lam, Jarrett Byrum

Abstract BACKGROUND: Assessment of statistical and clinically meaningful change is useful for treatment planning, monitoring progress, and evaluating treatment response in clinical trials. Outcome studies often assess statistically significant change, percent change, or a specified point change as an indicator of improvement, which may not be clinically meaningful. For measures that are commonly used in clinical trials, assessing clinical efficacy of an intervention relative to a placebo or control condition statistical significance does not in itself provide concise information about a given intervention's clinically meaningful effects. The process of defining clinical significance remains a challenge. As an attempt to develop a standard method of estimating clinically significant change, we propose adoption of a two-part strategy: The first part of the strategy involves using the Reliable Change Index (RCI) or similar method of change. The second part involves use of examination of clinical significance (CS). RCI is whether patients changed sufficiently that the change is unlikely to be due to measurement unreliability. CS change takes the patient from a score typical of schizophrenia to a score typical of the "normal" population. Studying RCI and CS has moved the outcomes paradigm from studying treatment groups to studying individual change within those groups. Assessments must move beyond symptom focus and evaluate individuals with respect to the complex broader domains of their functional, real-world, lives in which clinically significant change is operationalized.

METHODS: Data on symptomatology, PANSS, from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) were analyzed, data on depressive symptoms, STAR*D and data in cognitive change, C-PATH were examined. Three methods of RCI (Jacobson-Truax, Edwards-Nunnally, and Hageman-Arindell methods), in addition to effect size change and standard error of measurement were compared to standard methodology used to assess change (pre to post change of at least 2 SDs from the original mean, specified percent change, and point reduction based on the measure (e.g., 4 point change in cognitive measure).

RESULTS: The three RCI methods, 29.73%, 31.08% and 52.70% showed reliable improvements in PANSS scores. Fro percent change, 22.97% showed greater than 20% improvement, 29.73% improved on the PANSS remission criteria, and only 8.11% showed improvement of 2 SDs from the mean. When comparing RCIs with standard methods of change, only 18.92% of standard methods of change improvement also resulted in RCI significant improvement. Regarding clinically meaningful improvement, the Hageman-Arindell method was most

concordant with all three RCI measures and with the percent improvement for PANSS and cognitive measures as this method differentially analyzes clinically meaningful change at the individual level and at the group level (i.e., obtaining proportions of patients who have reliably changed and passed the cutoff point).
CONCLUSIONS: Reliable and clinically significant change should be reported in articles to complement the more familiar group summary methods. Assessment of clinically meaningful change is useful for evaluating treatment response. Outcome studies often assess statistically significant change, which may not be clinically meaningful. Comparisons of the proposed methods of determining clinically significant outcomes to biomedical standards of clinical significance will help determine the validation of this procedure, and improve the precision and effectiveness of assessing change in clinical trials.

Learning Objectives

- The audience will be able to understand that percentage change from baseline should not be used in statistical analysis. Investigators reporting percentage change should use another method, and convert the results to a percentage change by using mean baseline scores.
- The audience will gain an understanding of new methods used to assess clinically significant change and how they compare to the standard change scores currently used.

Literature References

- Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther. 2004 Jan;27(1):26-35. PubMed PMID: 14739871.
- Vickers AJ. The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: a simulation study. BMC Med Res Methodol. 2001;1:6. Epub 2001 Jun 28. PubMed PMID: 11459516; PubMed Central PMCID: PMC34605.

INITIAL SEVERITY NOT RELATED TO ANTIDEPRESSANT BENEFITS OR PLACEBO RESPONSE: A PATIENT LEVEL DATA ANALYSIS FROM 34 RANDOMIZED CONTROLLED TRIALS

Jonathan Rabinowitz, Bar-Ilan University
Nomi Werbeloff, Francine Mandel, François Menard, Lauren Marangell, Shitij Kapur

Abstract A meta-analysis (1) cited more than 1500 times, and considered to be one of the most controversial psychology studies ever published (2) reported that the efficacy of antidepressant medications depends on the severity of initial depression scores. That analysis included data from 35 published and unpublished studies on fluoxetine, venlafaxine, nefazodone and paroxetine conducted between 1987 and 1999. Drug–placebo differences increased as a function of initial severity, attributable to decreased responsiveness to placebo among very severely depressed patients, rather than to increased responsiveness to medication.
The purpose of this analysis was to retest using patient level, as distinct from the previous meta-analysis that used only trial level data, the hypothesis that the relationship between initial severity and antidepressant efficacy is attributable to decreased responsiveness to placebo among very severely depressed patients, rather than to increased responsiveness to medication. In addition, we also tested the hypothesis by analyzing the trial level data.

Methods: We used patient and trial level data from 34 randomized placebo controlled trials (n=12,217) (1987-2007) of citalopram, duloxetine, escitalopram, quetiapine and sertraline from the NEWMEDS registry. This included all acute placebo controlled trials of major depressive disorder in non-enriched adult populations, sponsored or owned by Pfizer, Lilly, AstraZeneca and Lundbeck on these 5 compounds. Analysis of covariance of change from baseline on the HAMD (Hamilton Depression Scale) (in 3 studies HAMD was estimated based on the MADRS (Montgomery–Asberg Depression Rating Scale)) was examined testing for baseline HAMD, a dichotomous variable of placebo vs. active treatment and their interaction. A significant interaction of placebo vs. active treatment and baseline score would support the study hypothesis. To further test the hypothesis, linear and quadratic regression equations of baseline severity and change from baseline to endpoint were run separately for placebo and active treatment. A larger regression coefficient for placebo than active treatment would further support the hypothesis. As an alternative test, we compared effects for those patients with low, medium and high HAMD scores at baseline, respectively <=22, between 22 and 25 and above 25. A significant interaction of baseline group and placebo vs. active treatment and greater effects within placebo than active treatment groups would support the hypothesis.
Results did not support the hypothesis. Using patient level data there was no significant interaction of placebo vs. active treatment and baseline severity (p=.28). The linear and quadratic regression results were the same for both regression models and were almost the same for active treatment and for placebo (R2=.04, .037; respectively) showing a small increase in change from baseline as a function of baseline severity in both the active and placebo groups. The difference in active vs. placebo change from baseline between the lower, medium and high severity groups was not statistically significant (p=.18). Analyzing the data at the trial level to replicate the previous meta-analysis gave similar results to the patient level analysis.
Discussion: Baseline severity was not associated with a more pronounced change from baseline in the active vs. placebo treated patients. These results do not support those of the trial level data analyzed in the previous meta-analysis that called into serious question the efficacy of antidepressant medications for many persons.
Patient level data is more sensitive to measuring the effects in question than trial level data as it allows for adjusting each patient's change score by their baseline value and other patient level characteristics. The difference in compounds covered is not likely to explain the difference between these results and those of the meta-analysis. Caution is advised when examining positive relationships between baseline severity and symptom improvement as these are the result of regression to the mean.

Learning Objectives

- Participants will understand the association of baseline severity and antidepressant response.
- Participants will understand the difference between meta-analysis and using actual patient data.

Literature References

- Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med. 2008;5(2):e45.
- Jarrett, Christian (19 September 2014). The 10 most controversial psychology studies ever published. Research Digest. British Psychological Society. Retrieved 7 October 2014.

LETHALITY OF MEDICATIONS USED TO TREAT DEPRESSION IN OVERDOSE

J. Craig Nelson, University of California San Francisco
Daniel A. Spyker

Abstract Suicide remains the most serious consequence of depression. Unfortunately, the medications used to treat depression can be the vehicle for a fatal suicide attempt. When trazodone and the SSRIs were introduced, they appeared to be safer in overdose than the TCAs. In fact deaths associated with the second generation agents were often attributed to the ingestion of multiple agents. The American Association of Poison Control Centers maintains the National Poison Data System (NPDS) which has recorded single (and multiple) drug exposures, outcomes and reason for ingestion since 1983. These data can facilitate comparisons of the lethality of medications used in treating depression. White et al used a 5-year sample (2000-2004) from NPDS that suggested differences among the antidepressants (1); however, the small number of exposures for some agents limited the power of their comparisons. The objective of this study is to examine the lethality of antidepressant drugs in a large sample and include other agents often used to treat unipolar or bipolar depression such as the atypical antipsychotics and anticonvulsant agents.

Methods: The NPDS database was queried for single medication ingestions during the period 2000-2014 for antidepressants approved for use in the US, 5 atypical antipsychotics (aripiprazole, lurasidone, olanzapine, quetiapine, and risperidone), 4 anticonvulsant agents (carbamazepine, lamotrigine, oxcarbazepine, and valproic acid), and lithium. Four other agents often used in these patients (buspirone, benzodiazepines, gabapentin, and pregabalin) were included as were two combination products. Outcomes of the ingestions are coded in NPDS as fatal, major (life threatening medical events), moderate (significant medical issues), or less severe. Reporting rates for less severe outcomes have changed over time so these data were adjusted. Lethality rates per 10,000 exposures and 95% confidence intervals were calculated.

Results: During this 15 year period there were 1,010,614 exposures of 45 single products and 2 combination products that were fatal in 703 cases. The tricyclic agents are still the most lethal of the antidepressants with fatality rates ranging from 31 to 142 per 10,000 ingestions. Amitriptyline alone accounted for 37% of all deaths due to antidepressants. Four of the SSRIs (fluoxetine, sertraline, paroxetine, and escitalopram) had very low rates 0.79 to 1.34/10,000. Citalopram and fluvoxamine had significantly higher rates, 4.1 and 3.9/10,000 respectively. Lithium, bupropion, venlafaxine, quetiapine, and valproic acid had rates between 6.9-12/10,000. Data for all 47 medications and Forest Plots will be presented.

Table 1

Antidepressant Group	Total Exposures	Fatal Exposures	Fatalities/10,000	95% CI
Trazodone	85,828	11	1.28	0.64,2.29
SSRIs	250,754	40	1.60	1.14, 2.17
Mirtazapine	16,131	4	2.48	0.68,6.35
Benzodiazepines	375,261	119	3.17	2.63, 3.79
Atypical Antipsychotics	195,589	105	5.37	4.39, 6.5
Anticonvulsants	108,593	59	5.43	4.14, 7.01
SNRIs	53,213	36	6.77	4.74, 9.36
Bupropion	66,685	46	6.90	5.05, 9.20
Lithium	47,264	57	12.1	9.14, 15.6
MAOIs	1,259	3	23.8	4.92, 69.5
TCAs/Tetracyclics	60,673	219	36.1	32.5,41.2
Combination Products	692	3	43.3	8.95, 126

Conclusions: The lethality of overdose with the newer agents used to treat depression varies considerably. While the therapeutic value of these treatments has been shown, differences in lethality risk should be considered in drug selection.

Learning Objectives

At the conclusion of the presentation the participant will be able to:

- Cite the drugs most likely to result in lethal overdose.
- Identify the drug least likely to be lethal in overdose from within a class.

Literature References

- White NC et al. J. Med Toxicol 2008;4(4):238-250.
- Barbey JT, Roose SP. J. Clin Psychiatry 1998;59(suppl 15):42-48.

RANDOMIZED, PROOF-OF-CONCEPT TRIAL OF LOW DOSE NALTREXONE FOR PATIENTS WITH BREAKTHROUGH SYMPTOMS OF MAJOR DEPRESSIVE DISORDER ON ANTIDEPRESSANTS

David Mischoulon, Depression Clinical and Research Program, Department of Psychiatry
Lindsay Hylek, Alisabet Clain, Lee Baer, David Soskin, Jonathan Alpert, Maurizio Fava

Abstract Introduction: The management of depressive breakthrough during treatment of major depressive disorder (MDD) is a challenging and understudied area. Although the pathophysiology of antidepressant tachyphylaxis is not fully understood, low dose naltrexone (LDN) may represent a promising approach through a mechanism of reversal of dopamine (DA) receptor desensitization proposed by Bear and Kessler. We carried out a pilot double-blind randomized controlled study of LDN 1mg twice daily versus placebo augmentation in patients who relapsed on dopaminergic agents.

Hypothesis: Subjects with depressive breakthrough on an antidepressant regimen containing a pro-dopaminergic agent assigned to LDN (1 mg bid) will demonstrate a more robust clinical improvement compared to subjects receiving placebo.

Methods: 12 of a projected 36 patients (67% female, mean age = 45 [SD 12]) who relapsed on various antidepressants and other DA agents (including methylphenidate or amphetamine stimulants, dopamine agonists, bupropion, low dose aripiprazole [≤2.5mg/day], sertraline [≥150mg/day], or duloxetine) were randomized to either naltrexone 1mg bid (n=6) or placebo (n=6) augmentation for 3 weeks. Outcomes were assessed based on the Hamilton Depression Rating Scale (HAMD; 17 and 28-item versions), Montgomery-Asberg Depression Rating Scale (MADRS; 10 and 15-item versions), and Clinical Global Improvement Scale-Severity (CGI-S). Paired and independent samples t-tests

and their nonparametric counterparts (Wilcoxon's Rank Sum and Mann Whitney U tests) were used to examine and compare outcomes for each treatment arm. Effect sizes (ES) were calculated by Cohen's d.
Results: Intent-to-treat analysis was performed on 12 patients randomized thus far. HAMD-17 scores decreased from 21.2 (SD 2.0) to 11.7 (SD 7.8) for LDN (z=-2.21, p=0.027), and from 23.7 (SD 2.3) to 17.9 (SD 6.0) for placebo (z=-1.99, p=0.046), but the difference between treatment groups did not reach significance by Mann-Whitney U test (p=0.30; Cohen d=0.61). HAMD-28 scores decreased from 26.2 (SD 4.0) to 12.0 (SD 9.8) for LDN (z=-2.02, p=0.043) and from 26.3 (SD 2.6) to 19.8 (SD 6.6) for placebo (z=-1.58, p=0.11), and the difference trended to significance (Z=-1.66, p=0.097; d=1.15). MADRS-10 scores decreased from 30.4 (SD 4.9) to 12.2 (SD 8.4) for LDN (z=-2.02, p=0.043) and from 30.7 (SD 4.3) to 22.8 (SD 8.5) for placebo (z=-1.78, p=0.075), and the difference was significant (Z=-2.10, p=0.035; d=1.45). MADRS-15 scores decreased from 36.6 (SD 6.2) to 13.2 (SD 8.8) for LDN (z=-2.03, p=0.042) and from 36.7 (SD 4.2) to 26.0 (SD 10.0) for placebo (z=-1.99, p=0.046), and the difference was significant (Z=-2.11, p=0.035; d=1.49). CGI-S scores decreased from 4.3 (SD 0.5) to 3.0 (SD 1.1) for LDN (z=-2.07, p=0.038) and from 4.3 (SD 0.5) to 4.0 (SD 0.6) for placebo (z=-1.00, p= 0.32), and the difference trended to significance (Z= -1.86, p=0.064; d=1.22).
Discussion: LDN may be an effective augmentation for individuals with MDD who relapse on a regimen including dopamine enhancing agents. Confirmation in larger studies is necessary.

Learning Objectives

- Demonstrate the efficacy of augmentation of low-dose naltrexone (LDN) in patients with antidepressant tachyphylaxis.
- Review potential mechanisms of action of this augmentation strategy.

Literature References

- Dunlop BW, Nemeroff CB: The role of dopamine in the pathophysiology of depression. Archives of General Psychiatry 2007; 64:327-337.
- Willner P, Hale AS, Argyropoulos S: Dopaminergic mechanism of antidepressant action in depressed patients. Journal of Affective Disorders 2005; 86:37-45.

ALKS 5461 AS ADJUNCTIVE TREATMENT OF MAJOR DEPRESSIVE DISORDER: PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY (FORWARD-1) EVALUATING TWO TITRATION SCHEDULES

Sanjeev Pathak, Alkermes
Sanjeev Pathak, Asli Memisoglu, William Martin, Srdjan Stankovic, Bernard Silverman, Elliot Ehrich

Abstract Background: ALKS 5461, a fixed-dose combination of buprenorphine (BUP), a mu opioid partial agonist, and samidorphan (SAM), a mu opioid antagonist, has previously demonstrated antidepressive effect as adjunctive treatment in subjects with inadequate response to antidepressant therapy (ADT) and is being comprehensively evaluated in the FORWARD (Focused On Results With A Rethinking of Depression) clinical program. Aims of this study (FORWARD-1) were to assess the safety and tolerability of 2 titration schedules for ALKS 5461 treatment initiation and to explore efficacy of ALKS 5461 as adjunctive treatment to ADT.
Methods: Double-blind, two-arm parallel design, 8-week (wk) study in which eligible subjects were randomized in a 1:1 ratio to a 1-wk or 2-wk ALKS 5461 titration schedule. Subjects in the 1-wk titration group received ALKS 5461 (BUP/SAM ratio) 0.5 mg/0.5 mg on Days 1-3, 1 mg/1 mg on Days 4-7 and 2 mg/2 mg on Days 8-56. Subjects in the 2-wk titration group received ALKS 5461 0.5 mg/0.5 mg on Days 1-7, 1 mg/1 mg Days 8-14 and 2 mg/2 mg on Days 15-56. All subjects remained on stable doses of background ADT throughout the study. Incidence of adverse events (AEs) in the Safety Population (received ≥1 dose of ALKS 5461) was the primary tolerability and safety endpoint. Efficacy was explored as change from baseline (BL) in MADRS total score over 8-wks in subjects who received ≥1 dose of ALKS 5461 and had ≥1 MADRS post-BL assessment (tested with signed-rank test).
Results: 66 subjects (1-wk titration group: n=34; 2-wk titration group: n=32) were randomized and included in the Safety Population. In the 1-wk titration group, 27 subjects experienced ≥1 AE and 4 subjects discontinued treatment due to ≥1 AE. In the 2-wk titration group, 28 subjects experienced ≥1 AE and 7 subjects discontinued treatment due to ≥1 AE. Most common AEs were nausea, vomiting, constipation, and dry mouth. In both titration groups there was a clinically meaningful and statistically significant reduction in MADRS total score at Wk 1 (1-wk: p=0.0003; 2-wk: p<0.0001) that persisted over the 8-wk period with mean±SD changes from BL of -14.7±10 (p<0.0001) and -18.0±9.7 (p<0.0001) for the 1-wk and 2-wk groups. Subjects achieving response and remission at Wk 8 were 60.9% and 52.2%, respectively for the 1-wk group and 78.3% and 52.2%, respectively for the 2-wk group.
Conclusions: The similar tolerability profile with both the 1-wk and 2-wk titration regimens suggests that 1-wk titration was sufficient and that a longer titration period (2 wk) does not show additional benefit when initiating ALKS 5461 treatment. The improvement in depressive symptoms found in this study is consistent with previous studies and further expands the antidepressant effect of ALKS 5461 to 8 wks. The favorable tolerability profile combined with the rapid onset and continuous antidepressant effect support further study of ALKS 5461 as a novel and potentially important new adjunctive treatment for MDD.

Learning Objectives

- To describe the safety and tolerability of 2 titration schedules for treatment initiation of ALKS 5461.
- To identify efficacy and response outcomes of ALKS 5461 as adjunctive treatment of major depressive disorder.

Literature References

- Ehrich E, Turncliff R, Leigh-Pemberton R, Fernandez E, Jones R, Fava M: Evaluation of Opioid Modulation in Major Depressive Disorder. Neuropsychopharmacology 14 January 2015 [Epub ahead of print]
- Rush AJ, Trivedi MH, Wisniewski SR: Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. Am J Psychiatry 2006; 163:1905-1917

THE ASCP SURVEY OF PSYCHOPHARMACOLOGISTS' PRESCRIBING PATTERNS FOR MOOD DISORDERS

Joseph Goldberg, Icahn School of Medicine at Mount Sinai
Marlene Freeman, Richard Balon, Leslie Citrome, Michael Thase, John Kane, Fava Maurizio

Abstract Background: Optimal successive treatment decisions are not well-established after an initial medication nonresponse in major depressive disorder or bipolar disorder. While practice guidelines offer consensus-based expert treatment recommendations, little is known about "real world" pharmacology decision-making by practicing psychopharmacologists.
Materials and Methods: We surveyed via internet the national membership of the American Society for Clinical Psychopharmacology (ASCP) to study preferred pharmacotherapy strategies and factors that influence medication choices for patients with mood disorders.
Results: Surveys were returned by 154/752 ASCP members (20.5%). After nonresponse to a serotonin reuptake inhibitor (SSRI) in major depressive disorder, participants equally favored switching within or across antidepressant classes. After a partial response, adjunctive bupropion was the preferred intervention, followed by changing antidepressant classes. Atypical antipsychotic augmentation was only a fourth-line consideration, even though moderate or marked efficacy was perceived in most instances with olanzapine, aripiprazole and quetiapine. Respondents favored avoiding antidepressants in bipolar I patients with mixed/cycling features or prior antidepressant-associated mania/hypomania. In rapid cyclers, they advocated antidepressant cessation and preferred the use of atypical antipsychotics and lamotrigine. One-third of respondents made use of pharmacogenetic testing when choosing drug regimens. Nearly two-thirds used monoamine oxidase inhibitors (MAOIs) in their practices. About three quarters of pharmacologists in the past year referred patients for ECT, while about half referred patients for repetitive transcranial magnetic stimulation (rTMS), suggesting that ASCP members largely care for a particularly treatment resistant clinical population.
Conclusions: ASCP members who treat mood disorder patients largely report prescribing medications that mirror the evidence base, in consideration of the characteristics of definable clinical subpopulations.

Learning Objectives

- Recognize preferred first-line and sequential pharmacotherapies for major depression, bipolar depression, and anxious depression, and clinical monitoring practices as identified from a survey of ASCP members.
- Recognize points of convergence and divergence between prescribing practices of ASCP members and evidence-based treatment recommendations.

Literature References

- Fava M, Rush AJ. Current status of augmentation and combination treatments for major depressive disorder: a literature review and a proposal for a novel approach to improve practice. Psychother Psychosom 2006; 75(3): 139-153.
- Rush AJ, Wisniewski SR, Warden D, et al. Selecting among second-step antidepressant medication monotherapies: predictive value of clinical, demographic, or first-step treatment failures. Arch Gen Psychiatry 2008; 65: 870-880.

A PHASE 2, RANDOMIZED, OLANZAPINE-CONTROLLED STUDY OF THE SAFETY, TOLERABILITY, AND EFFICACY OF ALKS 3831 IN ADULTS WITH SCHIZOPHRENIA

Elliot Ehrich, *Alkermes, Inc.*
Christoph Correll, Peter Weiden, Ying Jiang, Sanjeev Pathak, Lauren DiPetrillo, William Martin, Anjana Bose, Srdjan Stankovic, Bernard Silverman

Abstract Background: ALKS 3831 is a combination of olanzapine (OLZ) and samidorphan, a novel mu-opioid antagonist. OLZ is one of the most effective antipsychotics currently available; however, its use is limited by its propensity to cause weight gain. Animal models of samidorphan showed marked attenuation of OLZ-induced weight gain. Consistent with these findings, early studies of ALKS 3831 in human subjects suggest the potential to attenuate weight gain associated with OLZ treatment.
Methods: Subjects with stable schizophrenia were randomized in a 1:1:1:1 ratio to receive daily OLZ + placebo or 3 different treatments with ALKS 3831 (OLZ + 5, 10, or 20 mg samidorphan) in a double-blind paradigm for 12-wks following a 1-wk lead in period of OLZ. The primary efficacy endpoint was change in Positive and Negative Syndrome Scale (PANSS) total score from baseline to Week 12 to test equivalence of antipsychotic efficacy of the 3 pooled ALKS 3831 groups vs. OLZ. The analysis was performed for the full analysis set (FAS1) which included all randomized subjects who received ≥1 dose of study drug and had ≥1 post-baseline PANSS assessment. The pre-specified secondary endpoint, percent change in weight over 12-wks, was evaluated in FAS1 (n=300) and the subset of subjects with observed weight gain during the 1-wk OLZ lead in period (FAS2, n=195). Safety and tolerability of ALKS 3831 relative to OLZ were assessed.
Results: The change from baseline in PANSS total score with ALKS 3831 was equivalent to OLZ (LS mean difference (SE): 0.6±0.9 (95% CI: -1.2, 2.5). Over 12-wks, treatment with ALKS 3831 demonstrated a 37% lower mean weight gain vs. OLZ alone in FAS1 ($p=0.006$) and a 51% lower mean weight gain vs. OLZ in FAS2 ($p<0.001$). The risk of weight gain of ≥10% of baseline weight with OLZ was 2.7 times that of ALKS 3831 (95% CI: 1.1, 6.7; $p=0.02$) in FAS1 and 4.1 times that of ALKS 3831 (95% CI: 1.4, 12.3; $p=0.008$) in FAS2. The most common adverse events (≥5%) in the pooled ALKS 3831 subjects relative to OLZ subjects were somnolence, sedation, and dizziness.
Conclusions: ALKS 3831 demonstrated efficacy equivalent to OLZ over the course of the 12-wk study. ALKS 3831 was associated with a clinically meaningful and statistically significant attenuation of weight gain compared to OLZ alone. ALKS 3831 was well-tolerated with a safety profile similar to OLZ, with the exception of lower weight gain. These data suggest that ALKS 3831 may be an important new treatment option for schizophrenia.

Learning Objectives

- To describe the efficacy of ALKS 3831 in relationship to olanzapine for treatment of schizophrenia.
- To describe the safety and tolerability profile of ALKS 3831, including effects on body weight, compared to olanzapine.

Literature References

- Stankovic S, Risinger R, de Somer M, Du Y, Zummo J, Corey L, Silverman B, Ehrich E: Safety and Efficacy of Aripiprazole Lauroxil. Poster session presented at: American Society of Psychopharmacology Annual Meeting; 2014 June 16 - 19; Hollywood, FL
- Lieberman JA, Stroup TS, McEvoy JP, et al: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209-1223

EFFICACY AND SAFETY OF BREXPIPRAZOLE, A NEW INVESTIGATIONAL SEROTONIN-DOPAMINE ACTIVITY MODULATOR, FOR TREATMENT OF SCHIZOPHRENIA

Ross Baker, *Otsuka*
Aleksandar Skuban, John Ouyang, Mary Hobart, Stephanie Pfister, Margaretta Nyalis, Raymond Sanchez, William Carson, Hans Eriksson, Robert D. McQuade

Abstract While the efficacy of second generation APs is generally similar in clinical trials, their adverse event (AE) profiles differ. Some of the AEs, including metabolic changes, activation AEs, or unwanted sedation, may negatively impact patient's functioning, overall health and willingness to stay on therapy.
Brexpiprazole is a new serotonin-dopamine activity modulator that acts as a partial agonist at serotonin 5-HT1A and dopamine D2 receptors with similar subnanomolar potency, and as an antagonist at serotonin 5-HT2A and noradrenaline alpha1B/2C receptors. It was designed to be a partial agonist at D2 receptors, but with lower intrinsic activity than the only currently available partial dopamine agonist, aripiprazole, in order to decrease likelihood of activating AEs that may be mediated through stimulation of D2 receptors. In addition, the balanced binding profile at 5-HT1A, 5-HT2A, and D2 receptors distinguishes its pharmacology from those of other currently available antipsychotics.
The efficacy and safety of brexpiprazole for treatment of patients with schizophrenia was evaluated in two large, randomized, double-blind, placebo-controlled Phase 3 trials. Both trials enrolled patients with acute exacerbation of schizophrenia and were of six-week duration. The primary endpoint was change from baseline in PANSS total score.
Brexpiprazole showed superior efficacy to placebo in both trials. Brexpiprazole was well tolerated, with lower rates of discontinuation due to AEs compared with placebo. In pooled data, incidences of insomnia and agitation in the brexpiprazole treatment groups were similar or lower than those observed in the placebo groups. The incidences of sedation and somnolence were also similar to those observed with placebo. The incidence of akathisia across effective doses was 5%-7% and 5% for placebo. In two long-term open-label extension studies, the mean weight gain at week 26 was 1.3kg and 2.0kg at week 52. No clinically meaningful changes in lipid profiles or glycemic parameters were observed.
Conclusion: Data from two adequate and well-controlled clinical studies provide evidence that brexpiprazole is efficacious and safe in treating patients with acute schizophrenia. Brexpiprazole was well tolerated, with notably low levels of insomnia, agitation, and sedation and lower rates of akathisia than seen in trials with other partial agonists. Over long-term, there was moderate increase in weight with no clinically relevant changes in metabolic parameters.

EFFICACY AND SAFETY OF ARIPIPRAZOLE LAUROXIL IN ACUTE EXACERBATION OF SCHIZOPHRENIA: RESULTS FROM A DOUBLE-BLIND PLACEBO-CONTROLLED STUDY

Leslie Citrome, New York Medical College
Steven Potkin, Robert Risinger, Yangchun Du, Amy Claxton, Robert Risinger, Jacqueline Zummo, Anjana Bose, Bernard Silverman, Srdjan Stankovic, Elliot Ehrich

Abstract Aripiprazole lauroxil (AL) is a novel LAI atypical antipsychotic currently in development for treatment of schizophrenia. Following injection, the biotransformation of AL involves enzymemediated hydrolysis to form N-hydroxymethyl-aripiprazole, which subsequently undergoes water-mediated hydrolysis to aripiprazole. The proprietary technology (LinkeRx®) utilized to develop AL allows for controlled release after injection and extends exposure to the active molecule. The technology, combined with AL's unique formulation, allows for multiple dose strengths and dosing intervals, which provides flexibility to allow for individualized patient care.
An international, multicenter, randomized, double-blind, placebo-controlled trial was conducted in which patients with schizophrenia (n=623) were randomized in a 1:1:1 ratio to receive gluteal IM injection of AL 441 mg, AL 882 mg or matching placebo (PBO) once-monthly for 12 weeks. The primary efficacy outcome was the change in Positive and Negative Syndrome Scale (PANSS) total score from baseline to Week 12. The Clinical Global Impression - Improvement (CGI-I) score at Day 85 was the secondary efficacy endpoint. The effect of AL on signs and symptoms of hostility and aggressive behavior was evaluated by the PANSS Hostility item (P7) and PANSS Excited Component (EC) subscale. The incidence of adverse events (AEs) was collected.
Statistically significant and clinically meaningful improvements in PANSS total score were demonstrated for both AL doses at study endpoint with PBO-adjusted difference of -10.9 ($p<0.001$) and -11.9 ($p<0.001$) for AL 441 mg and 882 mg, respectively. Statistically significant separation from PBO was observed early after AL treatment was initiated and was maintained throughout the study for PANSS total score and all PANSS subscale scores. Both AL doses had significantly better CGI-I scores at Day 85 compared to PBO ($p<0.001$) and the proportion of patients who were "very much" or "much improved" on the CGI-I was significantly greater with AL 441 mg and 882 mg vs. PBO ($p<0.001$). The PANSS responder rates (≥30% reduction in PANSS total score at Day 85) were significantly greater with AL 441 mg (35.7%; $p<0.001$) and 882 mg (34.8%; $p<0.001$) vs. PBO (18.4%). In the sub-population of patients with more severe symptoms (baseline median PANSS score >92), the observed PBO-adjusted change in PANSS total score at Day 85 was -14.7±3.5 for AL 441 mg ($p<0.0001$) and -16.6±3.4 for 882 mg ($p<0.0001$). The percentage of patients with >1 score on Item P7 was significantly lower for AL 441 mg (53.6%; $p=0.01$) and 882 mg (46.1%; $p<0.001$) vs. PBO (66.3%). Clinically meaningful and statistically significant improvement were also seen with both AL doses in the PANSS EC subscale score with PBO-adjusted differences (mean±SE) of -1.97±0.40 ($p<0.001$) and -2.37±0.40 ($p<0.001$) in the AL 441 mg and 882 mg groups, respectively. The most common AEs (>5% of patients in either AL group) were akathisia, insomnia, headache and anxiety.
Both doses of AL demonstrated robust efficacy in patients experiencing an acute exacerbation of schizophrenia. In the sub-population of patients with more severe symptoms, improvements were found with both AL doses with larger observed effect sizes compared to the overall study population. AL was also associated with a significant reduction in symptoms of hostility and agitation. Both doses of AL were generally safe and well tolerated with a side effect profile consistent with oral aripiprazole.

Learning Objectives

- Describe the efficacy, safety, and tolerability profile of aripiprazole for treatment of schizophrenia.
- Identify the effect of aripiprazole lauroxil on symptoms of agitation and hostility in patients with schizophrenia.

Literature References

- Remenar JF. Making the leap from daily oral dosing to long-acting injectables: lessons from the antipsychotics. Mol Pharm. 2014;11(6):1739-49.
- Meltzer, H.Y., Risinger, R., Nasrallah, H.A., Du, Y., Zummo, J., Corey, L., Bose, A., Stankovic, S., Silverman, B.L, Ehrich, E.W., 2015. A randomized, double-blind, placebocontrolled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. J. Clin. Psychiatry. In press.

RESULTS FROM QUALIFY, A HEAD-TO-HEAD CLINICAL STUDY OF ARIPIPRAZOLE ONCE-MONTHLY AND PALIPERIDONE PALMITATE IN SCHIZOPHRENIA

Steven Potkin, University of California - Irvine, School of Medicine

Jean-Yves Loze, Carlos Forray, Ross A. Baker, Christophe Sapin, Timothy Peters-Strickland, Maud Beillat, Anna-Greta Nylander, Peter Hertel, Henrik Steen Andersen, Anna Eramo, Karina Hansen, Dieter Naber

Abstract Introduction: The QUALIFY study compared treatment effectiveness of aripiprazole once-monthly 400 mg (AOM 400) and paliperidone palmitate once-monthly (PP) in schizophrenia.
Methods: QUALIFY was a 28-week, randomized, open-label, rater-blinded, head-to-head study (NCT01795547) of 2 atypical long-acting injectable antipsychotics (LAIs), AOM 400 and PP (flexible dosing 50-150 mg/month as paliperidone [EU and Canada], or equivalent 78-234 mg/month as paliperidone palmitate [US]) that evaluated effectiveness in patients with schizophrenia. Included patients were ages 18–60 years needing a change from current oral antipsychotic treatment for any reason and, in the investigator's judgment, would benefit from LAI treatment. Patients were randomized to a 3-week conversion to oral aripiprazole or oral paliperidone followed by initiation of LAI treatment with AOM 400 or PP according to their labels (5 weeks) and continued with injections every 4 weeks for 20 weeks. The primary endpoint was change from baseline to week 28 in total score on the rater-blinded Heinrichs-Carpenter Quality-of-Life Scale (QLS), a validated measure of health-related quality of life and functioning, analyzed with a mixed model for repeated measures. The study was designed to test non-inferiority of the primary endpoint, followed by superiority testing if the 5-point non-inferiority margin was met. Additional endpoints included the Investigator's Assessment Questionnaire (IAQ), Clinical Global Impression-Severity (CGI-S) scale, Tolerability and Quality of Life Questionnaire (TooL), Work Readiness Questionnaire (WoRQ), and Subjective Well-being Under Neuroleptic Treatment-short form (SWN-S) scale. Pre-specified analyses assessed QLS domain scores, as well as primary and secondary endpoints in subgroups stratified by age (≤35 or >35 years).
Results: Of 295 randomized patients, 67.6% (100/148) in the AOM group and 56.5% (83/147) in the PP group completed 28 weeks of treatment. In treated patients, adverse events (AEs) were the most frequent reason for discontinuation (AOM: 11.1% [16/144], PP: 19.7% [27/137]). At week 24, mean ±SE dose was 387±3.4 mg AOM and 110±3.6 mg PP as paliperidone. The between-group least squares mean (LSM) difference in change from baseline to week 28 in QLS total score was 4.67 (95%CI:[0.32;9.02], p=0.036), confirming non-inferiority and establishing superiority of AOM 400 compared with PP. The respective LSM changes were 7.47±1.53 for AOM 400 (baseline 66.0±21.7) and 2.80±1.62 for PP (baseline 62.9±21.5). AEs occurring in the treatment continuation phase at rates ≥5% in either group were weight increased (AOM 400: 12/119 [10.1%]; PP: 17/109 [15.6%]), psychotic disorder (AOM 400: 3/119 [2.5%]; PP: 6/109 [5.5%]), and insomnia (AOM 400: 3/119 [2.5%]; PP: 6/109 [5.5%]). LSM treatment differences for additional outcomes including CGI-S, IAQ, QLS domains, WoRQ, TooL, and SWN-S, significantly or numerically favored AOM over PP, and improvements with AOM 400 were greatest in patients 35 years or younger.
Conclusions: Superior improvements on health-related quality of life and functioning as measured by the clinician-rated QLS, IAQ, CGI-S, and WoRQ, as well as numerically greater improvement on the TooL and SWN-S, and lower rates of all-cause discontinuation, suggest greater overall effectiveness for AOM 400 vs PP.

Learning Objectives

- To understand the primary and secondary results of the QUALIFY study, a head-to-head, randomized, open label study comparing real world effectiveness of aripiprazole once-monthly to paliperidone palmitate in patients with schizophrenia.
- To describe how the Heinrichs-Carpenter Quality of Life Scale measures health-related quality of life and functioning in patients with schizophrenia.

Literature References

- Heinrichs DW, Hanlon TE, Carpenter WT, Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. Schizophr Bull. 1984;10(3):388-98.
- Potkin SG, Bugarski-Kirola D, Edgar CJ, Soliman S, Le Scouiller S, Kunovac J, Miguel Velasco E, Garibaldi GM. Psychometric evaluation of the Work Readiness Questionnaire in schizophrenia. CNS Spectr. 2014 Oct 1:1-8.
- Jones PB, BarnesTR, Davies L, et al. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry 2006;63:1079-87.

A NEW TOOL TO AID PHYSICIANS AND THEIR PREGNANT PATIENTS – THE PHYSICIAN REFERENCE GUIDE FOR THE TREATMENT OF DEPRESSION IN PREGNANCY WITH ANTIDEPRESSANT MEDICATION

Sophie Grigoriadis, Sunnybrook, University of Toronto
Patricia Mousmanis, Emily H. VonderPorten, Lana Mamisashvili, Cindy-Lee Dennis, Gideon Koren, Meir Steiner, Amy Cheung, Lori E. Ross

Abstract Objectives: Antenatal depression is often undertreated. We developed a knowledge translation tool, synthesizing research to facilitate evidence based discussions for the treatment of depression during pregnancy and piloted our "Reference Guide" with end users.
Methods: The tool was synthesized using our published meta-analytic work on pregnancy, delivery and maternal outcomes associated with antenatal depression and antidepressant exposure. Feedback was provided on the Guide in two pilot phases and incorporated into the final version.
Results: Based on our previous work, antenatal antidepressant exposure was found to be modestly associated with cardiac malformation risk (but not overall congenital risk). Exposure was also associated with several delivery outcomes including preterm delivery, poor neonatal adaptation syndrome and persistent pulmonary hypertension of the newborn. Antenatal depression itself was found to be associated with preterm birth and less breastfeeding initiation. The aforementioned results among others were included in the tool. Clinical versus statistical consideration in the aforementioned outcomes is paramount. The initial pilot of the tool included 35 participant end users (psychiatrists (PSY), obstetricians (OB), family physicians (FMD), and non-prescribing practitioners). 95.5% found it "very useful/useful"; 77.3% were "very likely/extremely likely" to use the tool in their clinical practice. The second pilot included 53 uses of the tool by 24 participant end users (21 uses by FMD, 22 PSY, 10 OB). Data from different forms of feedback converged. Overall, end users referred to specific sections of the tool as needed in about 10 minutes. Most reported the sections that summarize the impact of antidepressants and depression as most helpful and important. The tool was perceived to improve the interactions with patients by 86% of the participants and that they would continue to use it. Most commonly, the tool was perceived to enable more comprehensive and evidence based discussions and 91% would recommend it to colleagues. The tool was revised based on feedback and the final version for dissemination will be presented.

Conclusions: Our knowledge translation tool summarizes risks of antenatal depression and antidepressant medication exposure. It facilitates treatment discussions and the clinical encounter, supporting clinicians and their patients. It has the potential to improve the quality and consistency of mental health care for perinatal women.

Learning Objectives

- Appreciate the variables to be considered for treatment discussions regarding depression during pregnancy.
- Learn about a Reference Guide for the treatment of depression during pregnancy.

Literature References

- Graham ID, Logan J, Harrison MB, Straus SE, Tetroe J, Caswell W, Robinson N: Lost in knowledge translation: Time for a map?. J Contin Educ Health Prof 2006; 26:13-24
- Grigoriadis S, VonderPorten EH, Mamisashvili L, Roerecke M, Rehm J, Dennis CL, Koren G, Steiner M, Mousmanis P, Cheung A, Ross LE: Antidepressant Exposure During Pregnancy and Congenital Malformations: Is There an Association? A Systematic Review and Meta-Analysis of the Best Evidence. J Clin Psychiatry 2013; 74:e293-e308

LURASIDONE FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER WITH MIXED FEATURES: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED 6 WEEK TRIAL

Josephine Cucchiaro, Sunovion Pharmaceuticals

Trisha Suppes, Robert Silva, Yongcai Mao, Josephine Cucchiaro, Caroline Streicher, Antony Loebel

Abstract Introduction: DSM-5 introduced a "with mixed features" specifier for major depressive disorder (MDD) when subthreshold manic or hypomanic features are present. Mixed features have been estimated to occur in 20-40% of patients with MDD. There are no established treatments for this patient population; standard antidepressants have not been demonstrated to be effective, and may worsen course and outcome.1 The aim of the current study was to evaluate the efficacy and safety of lurasidone in patients with MDD presenting with mixed (subthreshold hypomanic) features.

Methods: In this multi-regional study, conducted in the US and Europe, patients were required to meet DSM-IV-TR criteria for MDD, with a Montgomery-Asberg Depression Rating Scale (MADRS) score ≥26, and to be experiencing 2 or 3 DSM-5 mixed features criteria manic symptoms on most days over at least the 2 weeks prior to screening. Patients with any lifetime history of bipolar I manic episodes, or any mixed manic episodes, were excluded. Eligible patients were randomized to 6 weeks of double-blind treatment with either flexible doses of lurasidone 20-60 mg/d or placebo. Changes from baseline in MADRS total score (primary assessment) and Clinical Global Impression, Severity (CGI-S, key secondary assessment) scales were analyzed using a mixed model for repeated measures (MMRM) analysis. A sequential testing procedure was used to control the overall Type I error. Responder rates (≥50% reduction from baseline in MADRS total score) were analyzed using logistic regression.

Results: Patients were randomized to lurasidone (N=109; baseline MADRS, 33.2), or placebo (N=100; baseline MADRS, 33.3). Treatment with lurasidone was associated with significantly greater improvement compared with placebo from Weeks 2 through 6 on both the MADRS total score and CGI-S score. At Week 6, LS mean change for lurasidone vs placebo on the MADRS total score was (-20.5 vs –13.0; P<0.001; effect size, 0.80), and on the CGI-S score was (-1.83 vs –1.18; P<0.001; effect size, 0.60). Week 6 responder rates, for lurasidone vs placebo, were 67.6% vs 33.0%; P<0.001; NNT=3. The incidence of adverse events resulting in discontinuation was 2.8% and 5.0%, respectively on lurasidone and placebo. Nausea was the only adverse event that occurred with an incidence ≥5% on lurasidone (and greater than placebo) (6.4% vs 2.0%). Treatment with lurasidone vs placebo was associated with the following endpoint changes in mean weight (+0.67 kg vs. +0.37 kg, respectively), median total cholesterol (+0.5 mg/dL vs. -1.0 mg/dL), triglycerides (-4.0 mg/dL vs. +2.0 mg/dL), glucose (-1.0 mg/dL vs. +1.0 mg/dL), and prolactin (+1.7 ng/mL vs. -0.1 ng/mL).

Conclusions: In this study, the first ever placebo-controlled trial we are aware of in an MDD with mixed features population, lurasidone demonstrated significant efficacy at primary and all secondary endpoints. Lurasidone was well-tolerated, with an overall discontinuation rate that was lower than placebo. Minimal changes in weight, lipids and measures of glycemic control were observed.

Clinicaltrials.gov identifier: NCT01423240. Sponsored by Sunovion Pharmaceuticals, Inc.

Learning Objectives

- After completion of this presentation, the reader will have a better understanding of the clinical presentation of MDD with mixed features.
- After completion of this presentation, the reader will have a better understanding of the efficacy and safety of lurasidone in the treatment of MDD with mixed features.

Literature References

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC, 2013.
- Perugi G et al. The significance of mixed states in depression and mania. Curr Psychiatry Rep. 2014;16:486-93.

PHYSIOLOGIC AND CLINICAL EFFECTS OF L-METHYLFOLATE SUPPLEMENTATION IN SCHIZOPHRENIA: A RANDOMIZED CONTROLLED TRIAL

Joshua Roffman, Harvard Medical School/Massachusetts General Hospital

Liana Petruzzi, Alexandra Tanner, Hannah Brown, Hamdi Eryilmaz, New Fei Ho, Madeline Giegold, Noah Silverstein, Eugene Laska, Dara Manoach, Jordan Smoller, David Henderson, Donald Goff

Abstract Background: Folic acid supplementation confers modest benefit in schizophrenia, but its effectiveness is influenced by common genetic variants in the folate pathway that hinder conversion to its active form. We examined physiologic and clinical effects of L-methylfolate, the fully reduced and bioactive form of folate, in schizophrenia.

Methods: In this randomized, double-blind, placebo-controlled trial, medicated outpatients with schizophrenia received oral L-methylfolate 15 mg or placebo daily for 12 weeks. Patients were maintained on a stable dose of their previous antipsychotic medications. The primary outcome was change in plasma methylfolate level at 12 weeks. Secondary outcomes included change in symptoms (PANSS, SANS, Calgary Depression Scale for Schizophrenia), cognition (MATRICS composite) and three complementary MRI measures (working memory-related activation, resting-state connectivity, and cortical thickness). Analyses covaried for six genetic variants in the folate pathway previously associated with symptom severity and/or response to folate supplementation.

Results: Of 55 randomized patients (29 L-methylfolate, 26 placebo), 25 in each group completed the trial. Compared to placebo, L-methylfolate increased plasma methylfolate levels (mean difference=446 nmol/l, 95% C.I.=197 to 695 nmol/l, p=.0009) and improved PANSS total (mean difference=-6.1, 95% C.I.=-11.6 to -0.6, p=.03) as well as PANSS general and negative subscales. No changes were seen in SANS, depression, or cognitive composite scores. Post hoc examination of genotype x treatment interactions indicated significant effects of MTR 2756A>G genotype on change in PANSS total and general psychopathology scores. Patients receiving L-methylfolate exhibited convergent changes in ventromedial prefrontal physiology, including increased task-induced deactivation, reduced limbic connectivity, and increased cortical thickness.

Conclusion: L-methylfolate supplementation was associated with salutary physiologic changes and clinically significant symptomatic improvement in this initial study of schizophrenia patients, warranting larger clinical trials. ClinicalTrials.gov, NCT01091506.

Learning Objectives

- To appreciate the rationale for methylfolate supplementation in schizophrenia.
- To describe clinical and physiological effects of methylfolate supplementation in schizophrenia.

Literature References

- Roffman JL, Lamberti JS, Achtyes E, Macklin EA, Galendez GC, Raeke LH, Silverstein NJ, Smoller JW, Hill M, Goff DC. Randomized multi-center investigation of folate plus vitamin B12 supplementation in schizophrenia. JAMA Psychiatry 70:481-489, 2013.
- Brown HE, Roffman, JL. Vitamin supplementation in the treatment of schizophrenia. CNS Drugs, 28:611-622.

AGE DIFFERENCES IN INSTRUMENTAL ACTIVITIES OF DAILY LIVING ASSESSED USING THE VIRTUAL REALITY FUNCTIONAL CAPACITY ASSESSMENT TOOL (VRFCAT)

Alexandra Atkins, NeuroCog Trials

Nathan Spangola, Vicki G. Davis, Ioan Stroescu, Richard S.E. Keefe

Abstract Introduction: Reliable evaluation of both cognitive performance and functional capacity is critical to the effective assessment of mental health in aging individuals at risk for MCI/AD. Although cognitive assessment is largely standardized with the use of performance-based neuropsychological instruments, evaluation of functional capacity relies heavily on partner-reported measures that lack sensitivity to subtle functional deficits in preclinical MCI/AD (Sikkes et al., 2009; Gomar et al., 2011). Increasing interest in clinical trials for primary prevention and early intervention highlights the need for instruments that are sensitive to functional capacity deficits in healthier, non-demented individuals.

The Virtual Reality Functional Capacity Assessment Tool (VRFCAT) was developed as a direct performance-based assessment of functional capacity that is sensitive to changes in function across multiple populations. Using a realistic virtual reality environment, the VRFCAT assesses a subject's ability to complete instrumental activities associated with a shopping trip, including searching the pantry at home, making a list, taking the correct bus, shopping in a store, paying for the purchases, and returning home. In previous studies, the VRFCAT has demonstrated high test-retest reliability and has shown sensitivity to functional impairment (Ruse et al., 2014).

The primary aims of the present investigation were to (1) examine age-related differences in VRFCAT performance to assess the sensitivity of the measure to functional declines associated with normal aging, (2) explore the relationship between VRFCAT performance and cognitive function in both young and older adults, and (3) assess test-retest reliability of the VRFCAT for potential use as a co-primary measure of functional capacity in healthy aging and preclinical MCI/AD.

Methods: Participants included 44 healthy Young Adults (YA) ages 18-30 (24 male, 20 female), and 39 healthy Older Adults (OA) ages 55-70 (14 male, 25 female) who completed the VRFCAT at two visits. Subjects also completed the UPSA-2-VIM, a standard rater-administered performance-based measure of functional capacity utilizing physical props and materials. Cognitive performance was assessed using the MATRICS Consensus Cognitive Battery (MCCB) which assesses speed of processing, attention, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition.

Key outcome measures for the VRFCAT included total time to complete all objectives as well as total errors and forced progressions, which occur following repeated failure at a given task. Analyses examined age differences in performance as well as correlations between functional and cognitive outcomes.

Results: Results demonstrated strong age-related differences in performance on each VRFCAT outcome measure, including total completion time, total errors, and total forced progressions ($p<.001$ for all). VRFCAT performance showed strong correlations with cognitive performance across both age groups, including negative correlations between working memory and total errors on the VRFCAT ($r= -.46$ in YAs and $r= -.60$ in OAs, $p<.01$ for both). In OAs but not YAs, declines in verbal learning (HVLT total learning) and visual learning (BVMT total learning) were associated with a significant increase in the number of reminders required during the VRFCAT assessment (i.e. checking the bus schedule). In addition, compared to YAs, OAs demonstrated significantly stronger correlations between processing speed and VRFCAT total errors ($r=.49$ for OA vs. $r=-.06$ for YAs, $z=2.18$, $p<.05$). Although UPSA performance was not sensitive to differences between age groups ($p>.1$), UPSA total score was strongly correlated with VRFCAT performance in both groups, suggesting that both measures are assessing similar constructs. VRFCAT Total Time demonstrated strong test retest reliability (ICC=.78 for OAs and ICC=.62 in YAs) and small, insignificant practice effect, indicating the measure is suitable for repeated testing in healthy aging populations.

Conclusions: The assessment of functional capacity in primary prevention and preclinical/prodromal AD trials requires measures with improved sensitivity to changes in non-demented individuals. Results from the present investigation suggest the VRFCAT is sensitive to age-related differences in functional capacity and provide preliminary support for the VRFCAT as a co-primary measure.

Learning Objectives

- Communicate the need for improved measures to assess functional capacity in non-demented preclinical AD populations.
- Introduce the VRFCAT as a potential co-primary tool for assessing instrumental activities of daily living in clinical trials.

Literature References

- Sikkes SA, De Lange-De Klerk ES, Pijnenburg YA, Scheltens P, Uitdehaag BM. A systematic review of instrumental activities of daily living scales in dementia: room for improvement. J. Neurol. Neurosurg. Psychiatry. 2009;80(1):7–12.
- Ruse SA, Harvey PD, Davis VG, Atkins AS, Fox,C., Keefe RS. Virtual Reality Functional Capacity Assessment in Schizophrenia: Preliminary data regarding feasibility and correlations with cognitive and functional capacity performance. Schizophrenia Research on Cognition, 2014; 1(1): 21-26.

4:30 p.m. - 6:30 p.m.
Special Session/Workshop

HOW TO USE THE MODEL PSYCHOPHARMACOLOGY CURRICULUM IN VARIOUS TEACHINGS

Ira Glick, Stanford University School of Medicine

Overall Abstract This workshop will focus on how to teach cutting edge clinical psychopharmacology for a) psychiatric residents, b) primary care physicians, c) medical students in US and globally. The target audience is program directors, Chairs, and teachers of psychopharmacology and psychiatry. Workshop faculty includes David Osser, Harvard; and Ira Glick, Stanford.

NCCAM WORKSHOP ON GUT MICROBES AND THE BRAIN: WHAT WE KNOW AND WHERE WE'RE GOING

Emmeline Edwards, National Institutes of Health/NCCAM

Overall Abstract Gut microbiota are increasingly recognized as influencing many aspects of human health. Indeed, the NIH large-scale metagenomic Human Microbiome Project is allowing the role of microbiota in health and disease to take centre stage. In particular, there has been growing interest in examining the role these microbes play in modulating brain function, brain chemistry, and behavior and, conversely, the role of the CNS (e.g., HPA-axis) plays in modulating the microbiome through the gut-brain axis. It is known that prebiotics, probiotics, antibiotics and diet can modulate the gut microbiota and that could in turn affect brain function. Clinical observations showing co‐ morbidity between stress and anxiety and gastrointestinal disorders further suggests that changes in microbiota may influence susceptibility to anxiety, depression, and other brain-related disorders. The gut–brain axis, therefore, may be an important, novel system to target for the development of novel treatments for many brain-related disorders such as mood and anxiety disorders. This NCCAM/NIH sponsored symposium will review research focusing on how changes in microbiota can impact behavior and brain physiology in animals and in humans, and will offer a rationale for future translational research on microbial-based CNS therapeutics. The following presentations will highlight the potential pathways for microbiota brain communication and the bi-directional impact of enteric microbiota and CNS function: 1) Dr. John Williamson (National Institutes of Health/NIH) will discuss rational basis for probiotic manipulations and ecologic principles in host-microbe relationships as a human microbiome-brain-gut systems biology view; 2) Dr. Melanie Gareau (University of California San Diego) will provide an overview of the underlying mechanisms by which the microbiota-gut-brain-axis exerts its effect on the CNS. She will focus on the importance of the gut-brain axis on cognitive function; 3) Dr. Kirsten Tillisch (University of California Los Angeles) will review the evidence that both central and peripheral mechanisms involved in visceral pain perception and anxiety can be affected by intestinal microbiota. She also will present data on gut microbiome brain signaling in healthy human subjects.

Learning Objectives

- Participants will get an overview of the potential mechanisms associated with the microbiome-brain–gut axis.
- The potential impact of these mechanisms will be discussed in the context of health and disease.

THE PERINATAL WOMAN AND PSYCHOPHARMACOLOGY: OPTIMIZING DOSING AND INFANT OUTCOMES

Crystal Clark, Northwestern University

Overall Abstract Purpose: Many childbearing women with mood disorders must continue psychotropic medications in pregnancy. Despite this reality, physicians are often challenged with how to best manage medication treatment across pregnancy and postpartum. This workshop will present data on the use of antiepileptic drugs (AEDs), selective-serotonin reuptake inhibitors (SSRIs), and atypicals in pregnancy and clinical considerations on management of illness and infant outcomes.
Content: Dr. Crystal Clark will focus on optimization of dosing in pregnant and postpartum women with bipolar disorder. She will present new data from her novel pharmacokinetic investigation of lamotrigine (LTG) concentrations in pregnancy and postpartum. Based on this data she will discuss guidelines on optimizing wellness as it relates to dosing LTG in pregnancy and postpartum. This novel data underscores the utility of personalized therapeutic dose monitoring for pregnant women on psychotropic medications.
Dr. Elizabeth Gerard will discuss use of AEDs in the pregnant patient from the neurologist's perspective. Although psychiatrists commonly use antiepileptic drugs, most research on AEDs in pregnancy has been led by neurologists. Dr. Gerard will provide valuable perspective on the use of antiepileptic drugs across pregnancy including infant outcomes.
Dr. Katherine Wisner will present data on the impact of depression and SSRI antidepressant treatment during pregnancy on fetal and infant outcomes. She will also discuss the concentration changes of SSRIs across pregnancy and implications for treatment. SSRIs are increasingly prescribed in pregnant and lactating mothers, knowledge of outcomes and physiological effects of pregnancy on medication concentration is essential for effective treatment.
Dr. Dorothy Sit will present data on maternal mood disorders and gestational diabetes. She will discuss infant outcomes and gestational diabetes as it relates to psychotropics in pregnancy, specifically atypicals. Gestational diabetes increases the risk of adverse birth outcomes. It is important to consider the risk of gestational diabetes in women with mood disorders in order to reduce risk of poor infant outcomes.
Methodology (in the order presented above): longitudinal pharmacokinetic analysis of LTG disposition across pregnancy; review of data on AEDs, recommendations for dosing, and infant outcomes; comparison of data on infant outcomes of healthy controls to depressed pregnant women with and without SSRI exposure and review of changes in SSRI concentrations across pregnancy; comparison of glucose challenge test (GCT) levels in healthy pregnant controls vs. women with depression or bipolar disorder and the use of atypical antipsychotics.
Results: decrease in LTG concentration across pregnancy requires increased dosages in pregnancy; use of AEDs in childbearing women must consider infant outcomes and dosing; growth outcomes are similar in depressed SSRI-treated and untreated pregnant women and SSRIs require increased dosing in some women during pregnancy depending on individual metabolic characteristics; use of medications associated with weight gain is increased in bipolar disorder and increase GCT levels are associated with increased adverse infant outcomes.
Importance: Wellness for mother and baby depends upon knowledgeable physicians equipped with the latest evidenced based data to inform the risk benefit analysis of medication management in pregnancy and postpartum.

Learning Objectives

- Participants will be able to describe the current available data on infant outcomes as it relates to use of psychotropic medications in pregnancy.
- Participants will be able to characterize how pregnancy impacts concentration of some psychotropic medications in pregnancy and the clinical recommendations to maintain drug efficacy and reduce negative outcomes.

Wednesday, June 24, 2015

8:15 a.m. - 9:45 a.m.
Keynote/Plenary

CHANGING THE PARADIGM FROM DIAGNOSE AND TREAT TO PREDICT AND PREEMPT

Chair: Husseini Manji, Janssen Research & Development, LLC

Overall Abstract Traditionally therapies have been developed for intervention in clinically diagnosed patients with established pathologies and overt symptoms. There are many drivers for this paradigm, including the facility of performing clinical trials in easy to identify populations with room to show clinical improvement, and patients to adhere to therapies that address clear and present deficits. However, it is clear that to have markedly improved outcomes for individuals suffering from serious neuropsychiatric illnesses, we believe that interventions will need to move earlier in the disease continuum, with the ultimate goal of shifting from the current 'diagnose and treat' to a 'predict and preempt' paradigm. In most neurodegenerative diseases, due to the existence of 'cognitive reserve' and plasticity of synapses and circuits, clinically discernable symptoms appear much after considerable progression of underlying pathology, by which time irreversible cellular and physiological damage has already occurred. Likewise, other neuropsychiatric disorders are characterized by recurrences and relapses, each of which causes a precipitous, irreversible progression of pathophysiology. As a result, CNS diseases are particularly suitable for this shift towards 'disease interception' via earlier detection and treatment in prodromal stages or prediction and prevention of relapses and reoccurrences. While earlier disease interception can bring considerable value to individual patients, health-care systems and society at large, many challenges abound in the successful discovery, development and adoption of therapies that target earlier stages of disease. These challenges range from scientific – improved understanding of causative biological processes and means to diagnose them early, to regulatory – e.g. development of pathways that allow for approval of interventions which may show meaningful bending of the disease and 'cost of care' curve only years down the road. In this session we will explore these challenges and novel solutions that will allow us to intervene early and halt these diseases before they cause irreparable damage and devastation. The outstanding group of panelists will discuss novel technological approaches to facilitating disease interception, and early intervention approaches in a variety of neuropsychiatric conditions including autism, schizophrenia and recurrent mood disorders.

DATA AND INFORMATICS CHALLENGES IN MOVING FROM A 'DIAGNOSE AND TREAT' TO A 'PREDICT AND PREMPT' PARADIGM

Narayan Vaibhav, Johnson & Johnson

Abstract Neurodegenerative and psychiatric disorders are usually characterized by a prolonged asymptomatic phase that precedes appearance of overt symptoms. Successful intervention in these early stages requires characterization of the prodrome with regards to genetic risk and dysregulation in upstream pathways that drive disease pathophysiology. Early disease interception would require data-driven biosignatures of prodromal disease states, sensitive measures of disease state and treatment efficacy, predictive models of disease progression and a clearer understanding of disease subtypes that can be mechanistically targeted with novel therapies. Current models of prodromal stages of diseases like Alzheimer's, depression and schizophrenia are largely based on phenomenology and lack specificity or predictive value. Detailed characterization of prodromal populations via dense longitudinal phenotyping that incorporate environmental factors as well as molecular and neuroimaging readouts are required to identify at-risk populations and build prognostic models of conversion to clinically manifest disease. Knowledge of disease subtypes will enable identification of subpopulations that are not likely to respond to current therapies, and thus reduce the time between identification of prodromal illness and treatment with a novel interception therapeutic. In general, a more comprehensive approach that establishes a network of solutions related to diagnosis, predictive modeling of disease trajectory, efficacy monitoring, and adherence tools would be required to enable discovery, development, and clinical adoption of early interception therapies. This would require integration of data across long time-spans from predisease states to long-term efficacy and outcome data in established chronic diseases. Currently such data are collected by different entities and organizations and is often fragmented and siloed. For example, controlled-trials drug-efficacy data are largely the realm of pharmaceutical companies. Follow-on data on clinical care and outcomes are managed by hospital systems and health insurance companies. Data related to wellness and natural aging are less prevalent and even more fragmented. Going forward, we expect that increasing amounts of longitudinal data ranging from base-line genetics to late-stage disease outcomes will increasingly be owned and controlled by the patients themselves, while being made available to the healthcare system at large. As a new data ecosystem evolves, a robust framework related to data sharing, privacy and ownership will be required, if we are to realize the goal of early identification and interception of disease. In this talk we will explore, via specific examples, how some of these data related challenges may be addressed to hasten the transition from a 'diagnose and treat' to a 'predict and preempt' paradigm.

EARLY RISK DETECTION OFFERS PROMISE FOR ALTERING THE COURSE OF BRAIN AND BEHAVIORAL DEVELOPMENT IN AUTISM

Geraldine Dawson, Duke University

Abstract Recent prospective studies of infants at risk for autism spectrum disorder (ASD) have provided insights into very early development of children with autism and led to the development of novel screening approaches for identifying infants at risk for ASD. At the same time that early screening tools are being developed, new approaches to early intervention are being tested with infants as young as 6-12 months of age. The hope is that, by intervening very early in life, the course of early brain and behavioral development can be modified and the disabling symptoms of autism can be significantly reduced or even prevented.

THE RAISE STUDY: WHAT HAVE WE LEARNED?

John Kane, The Zucker Hillside Hospital

Abstract Early intervention in schizophrenia has been the focus of considerable attention with the hope that such efforts would improve overall outcome. The Early Treatment Program (ETP) study is part of the National Institute of Mental Health (NIMH) initiative called Recovery After an Initial Schizophrenia Episode (RAISE). RAISE aims to develop, test, and implement person-centered, integrated treatment approaches for FEP that promote symptomatic and functional recovery

The primary aim of RAISE-ETP was to compare the impact of NAVIGATE, a comprehensive, multidisciplinary, team-based treatment approach for first episode psychosis (FEP) designed for implementation in the context of the U.S. healthcare system, to clinician-choice Community Care (CC) on quality of life.

Thirty-four community treatment clinics in 21 states were randomly assigned to either provide NAVIGTE or CC. To obtain unbiased study evaluations, diagnosis, duration of untreated psychosis (DUP) and clinical outcomes were assessed via live, two-way video by remote, centralized raters masked to study design and treatment allocation. Four hundred and four participants (mean age 23) with schizophrenia-spectrum disorders and <6 months lifetime antipsychotic treatment were enrolled and followed for a minimum of two years. The primary outcome measure was the Total Score of the Heinrichs-Carpenter Quality of Life Scale (QLS).

Over the first 2 years, the 223 participants at NAVIGATE sites remained in treatment longer, experienced greater improvement in QLS, psychopathology and involvement in work or school compared to the 181 participants at CC sites. The sample median DUP was 74 weeks. NAVIGATE participants with DUP less than 74 weeks had greater improvement on quality of life and psychopathology compared with those with longer DUP and those in CC. Rates of hospitalization were low and did not differ between groups.

Comprehensive care for FEP can be implemented at community mental health clinics using existing financing strategies in the U.S. and improves functional and clinical outcomes. Effects are more pronounced for those with shorter DUP. Attention to strategies to reduce DUP could improve outcomes for patients early in the course of treatment.

FIRST STEPS: INITIAL EFFORTS TO DEVELOP PREVENTATIVE INTERVENTIONS FOR YOUTH AT RISK FOR BIPOLAR DISORDER

Ellen Frank, University of Pittsburgh School of Medicine

Abstract Probably the single most potent risk factor for the development of bipolar disorder is having a first-degree relative with bipolar disorder. Furthermore, those who have such a relative are likely to have an earlier onset and a more pernicious course. These facts signal both a tremendous challenge and a great opportunity. Early intervention has the potential to prevent or, at least delay, the onset of this highly debilitating illness. Given the consistent evidence that bipolar-specific psychosocial interventions add significantly to the efficacy of pharmacotherapy in those who already have bipolar disorder, several research groups have begun developing adaptations of these interventions to be used without pharmacotherapy in youth at risk for bipolar disorder.

This presentation will focus primarily on the work of Goldstein, Frank and colleagues at the University of Pittsburgh and the work of Miklowitz and colleagues at UCLA and Stanford in adapting treatments that have been shown to be efficacious in the treatment of bipolar disorders with the aim of preventing the onset of bipolar disorder in youth at risk on the basis of family history. The Pittsburgh group has focused on an adaptation of interpersonal and social rhythm therapy (IPSRT – Frank, 2005), while the UCLA/Stanford group has employed an adaptation of Family Focused Treatment (FFT-Miklowitz, 2008). The adaptations of the treatments for this population will be described, as will the initial outcomes from small randomized studies of each of these interventions.

10:00 a.m. – 12:00 p.m.
INSTITUTE DIRECTORS PLENARY

Chair: Michael E. Thase, Perelman School of Medicine at the University of Pennsylvania

Overall Abstract This year's Institute Director's Plenary session will bring together directors from various NIH institutes who all have a similar goal of searching for new approaches in the research of mental disorders. Each director will have ten minutes to discuss what activities are going on within their institute regarding this goal.

Steven Zalcman, representing NIMH, will begin the session discussing how to bend the curve in psychiatric therapeutics by leveraging advances in clinical neuroscience. Three major concepts will be highlighted: (1) Transforming diagnostics: as mental disorders are brain disorders, 21st century psychiatric diagnosis should be rooted in biology and behavior; (2) Transforming therapeutics: emphasizing an experimental medicine paradigm focused on target identification and validation, trials must be designed to be equally informative with positive or negative data; and (3) Transforming culture: shifting the culture from "my data" to data mining, the bywords being standardization, integration, and sharing.

Phil Skolnick, representing NIDA, will discuss the challenges of developing "other than abstinence" outcome measures in medication trials for substance use disorders (SUDs). At present, a period of sustained abstinence appears required for regulatory approval of a medication to treat stimulant (cocaine, methamphetamine), cannabis and nicotine use disorders. For alcohol use disorders, the FDA has adopted the "percentage of subjects with no heavy drinking days" as an endpoint for pharmacotherapy trials, indicating a potential path forward for developing analogous, non-abstinence endpoints for SUD trials. However, reductions in drug use per se (short of abstinence) must have prognostic value in order for the FDA to consider it as an acceptable basis for approval. Thus, even if a medication can sustain reductions in drug use, the challenge is to demonstrate that this "success" is accompanied by benefits that accrue in dimensions which will be readily

THE NIMH RESEARCH DOMAIN CRITERIA PROJECT (RDOC)

Steven Zalcman, National Institute of Mental Health/NIH

NIMH Update

Steven Zalcman, National Institute of Mental Health

Abstract Steven Zalcman, representing NIMH, will begin the session discussing how to bend the curve in psychiatric therapeutics by leveraging advances in clinical neuroscience. Three major concepts will be highlighted: (1) Transforming diagnostics: as mental disorders are

brain disorders, 21st century psychiatric diagnosis should be rooted in biology and behavior; (2) Transforming therapeutics: emphasizing an experimental medicine paradigm focused on target identification and validation, trials must be designed to be equally informative with positive or negative data; and (3) Transforming culture: shifting the culture from "my data" to data mining, the bywords being standardization, integration, and sharing.

NCCIH UPDATE

David Shurtleff, National Center for Complementary & Alternative Medicine (NCCAM)

Abstract Dr. Shurtleff will cover NCCIH research priorities and funding opportunities such as Multi-IC program announcement on Advancing Translational and Clinical Probiotic/Prebiotic and Human Microbiome Research and NICCH's Exploratory Clinical Trials of Mind and Body Interventions program announcements among other priorities and highlights.

NIDA UPDATE

Phil Skolnick, National Institute of Drug Abuse/NIH/DHHS

Abstract Phil Skolnick will discuss the challenges of developing "other than abstinence" outcome measures in medication trials for substance use disorders (SUDs). At present, a period of sustained abstinence appears required for regulatory approval of a medication to treat stimulant (cocaine, methamphetamine), cannabis and nicotine use disorders. For alcohol use disorders, the FDA has adopted the "percentage of subjects with no heavy drinking days" as an endpoint for pharmacotherapy trials, indicating a potential path forward for developing analogous, non-abstinence endpoints for SUD trials. However, reductions in drug use per se (short of abstinence) must have prognostic value in order for the FDA to consider it as an acceptable basis for approval. Thus, even if a medication can sustain reductions in drug use, the challenge is to demonstrate that this "success" is accompanied by benefits that accrue in dimensions which will be readily understood by physicians, patients, their families and of sufficient value to be reimbursed by third party payers.

NEW PROGRAMS TO SUPPORT THERAPY AND DEVICE DISCOVERY AND DEVELOPMENT IN NEUROLOGY

Rajesh Ranganathan, National Institutes of Health, National Institute of Neurological Disorders and Stroke

Abstract The Office of Translational Research (OTR) at the National Institute of Neurological Disorders and Stroke at the National Institutes of Health, facilitates the preclinical discovery and development of new therapeutic interventions for neurological disorders. The OTR offers six programs that support the design, implementation, and management of research activities to critical translational challenges in neurology. The programs include: 1) the Anticonvulsant Screening Program (ASP), 2) Blueprint Network (BPN), 3) The Countermeasures Against Chemical Threats Program (CA), 4) Cooperative Research to Enable and Advance Translational Enterprises (CREATE), 5) Innovation Grants to Nurture Initial Translational Efforts (IGNITE), and 5) The Small Business Innovation Research Program (SBIR). The OTR provides funding (approximately $100 million annually) in grants and resources to industry and university researchers to advance early-stage neurological technologies, devices, and therapeutic programs to industry adoption (i.e., investor funding and corporate partnerships). Significant emphasis is placed on engaging other stakeholders, such as pharmaceutical, biotechnology, venture capital, and patient advocacy organizations to ensure that projects are adequately de-risked to accelerate downstream investments and to develop much-needed therapies for people suffering from neurological disorders. The talk will provide overiews on these programs and how they can link to successful development outcomes.

3:45 p.m. - 5:45 p.m.
Workshops

HOW SHOULD WE DEFINE RESISTANCE IN DEPRESSION?

Maurizio Fava, Massachusetts General Hospital

Overall Abstract Inadequate response to antidepressant therapy is an extremely common occurrence in clinical practice. Over the past 30 years, countless trials have focused on pharmacological therapeutic options for depressed patients who have not responded to adequate, standard antidepressant therapies. Very few drug treatments, however, have consistently shown superiority over placebo in resistant depression. Methodologies used to identify such patients have varied greatly as there is no consensus on how to best design such studies. This workshop will review the methodologies used to define resistance to treatment in depression and the design and methodological issues that emerge in the context of studying treatment interventions in these populations. Dr. Trivedi will discuss various clinical approaches to the definition of resistance in depression and their clinical trial implications. He will also review the prevalence of resistance to drug treatment in depression and distinctions between different levels of inadequate response. Dr. Papakostas will present results of recent meta-analyses of studies in resistant depression, contrasting those using an open-label lead-in phase followed by a double-blind randomized phase with those using historical failures and immediate enrollment into a randomized trial. Dr. Fava will review results of studies that have enrolled patients with historical failures via independent confirmation of treatment history, and compared them with those of studies that have used historical failures without such confirmations. He will also put in methodological perspective results of these comparisons. Dr. Sanacora will review advantages and disadvantages of using biomarkers associated with treatment resistance in depression to enrich clinical trial populations. Finally, Dr.Farchione will provide discussion on the presentations, followed by Q&A.

Learning Objectives

- To become familiar with the various definitions of resistance to drug treatment in depression.
- To learn the most critical methodological issues involved in identifying the populations non-responsive to antidepressant therapy.

LONG ACTING INJECTABLES IN THE TREATMENT OF SCHIZOPHRENIA: MISSED OPPORTUNITIES AND CHALLENGES

Jean-Pierre Lindenmayer, New York University

Overall Abstract Successful management of patients with schizophrenia is complicated by a variety of real world factors, including low treatment adherence, comorbid substance abuse, unstable living conditions (eg, homelessness), multiple hospitalizations and more recently

contacts with the criminal justice system. These factors can complicate poor treatment adherence, which in turn can have direct public health implications both for patients and society at large due to violent behaviors, readmissions and incarceration. Long-acting injectable (LAI) antipsychotic therapies provide physicians with accurate monitoring of adherence and deliver predictable therapeutic concentrations continuously over several weeks and may represent better alternatives to oral treatments as they eliminate the need for potential conflicts over daily medication administration. However, LAI formulations are associated with a number of unresolved challenges. This workshop will explore a number of these challenges and discuss possible solutions and approaches using data obtained from recent clinical trials and audience participation to address the following questions: Why has the use of LAIs decreased in most clinical settings? What are the attitudinal barriers, which prescribers face when considering the use of LAIs? Is there a difference in efficacy and adherence results between oral antipsychotics and LAIs? Does the trial design influence comparative efficacy results when comparing oral antipsychotics and LAIs? How do we evaluate the efficacy of LAIs? Are there public health and economic consequences between the use of oral antipsychotics and LAIs? (1) Steve Potkin, MD will present data on the under-utilization of LAIs together with prescribers' opinions on their usefulness. He will further identify multiple barriers to the use of LAI experienced by physicians in today's diverse practice settings. He will review solutions and elaborate on newer approaches.. (2) Ira Glick, MD will evaluate and resolve the conflicting results in the recent literature of meta-analyses comparing the efficacy of oral antipsychotics and LAI treatment by clarifying the different research design issues underlying these results. He will discuss what elements are required in the design of trials with LAIs and choice of patient population together with the appropriate evaluation procedures (3) Larry Alphs, MD will review the design and results of a recent effectiveness trial comparing LAI with oral antipsychotics in patients who have been repeatedly incarcerated. He will discuss the rationale of the trial design, the rationale for choosing the targeted population, of combining both efficacy and effectiveness aspects in such trials. (4) Remal Bera, MD will focus on the economic impact on health care resource use after initiation of LAI antipsychotic medications. Based on a recently completed mirror image study of the use of LAI, he will demonstrate the potential savings which can be obtained by using LAIs in routine clinical care. Steve Marder, MD, the discussant, will review all four presentations and coordinate the audience discussion with the aim of developing some general lines for a better understanding of the appreciate use of LAIs.

Learning Objectives

- After this workshop particiopants will be familiar with barriers to the use of long acting injecatable antipsychotics (LAIs) and methods to overcome them.
- After this workshop participants will better understand and interpret research designs comparing the efficacy of LAIs to oral antipsychotics.

Thursday, June 25, 2015

8:30 a.m. - 10:00 a.m.
Panel Sessions

MIND THE GAP: SEARCHING FOR MEASUREMENTS TO MORE ACCURATELY MEASURE SYMPTOMS IN CNS TRIALS

Jan Sedway, inVentiv Health Clinical

Overall Abstract Advances in the scientific understanding of underlying pathological processes and improvements in imaging and biometric signal detection technologies has fostered a divergence in emphasis, or gap incurrent approaches to symptom measurement in CNS trials. We are all waiting for the precise panel of biomarkers to be discovered to identify Bipolar I disorder or predict who will progress to Alzheimer's disease and when. However, until these biomarkers are identified, validated to clinical presentation, and matched to treatment targets, clinical trial outcomes will remain largely dependent upon psychometric measurements. Unfortunately, the nature of psychometric measurements introduces multiple forms of variability not found in biomarker measurement.

Psychometric outcome measures in CNS trials often face challenges in terms of their validity, reliability, sensitivity, and specificity. Without accurate, sensitive and valid measures, the likelihood of a positive trial is extremely low. Further, for a multi-center trial and possibly even a multi-country trial, the scale must have the potential for high intra- and inter-rater reliability even when those administering the scale are clinicians with widely varying experience and expertise. The scale must be appropriate for use across regions, languages and cultures. All of these requirements make it very difficult to create and identify appropriate scales specifically targeted to measure the same thing that the compound being tested is intended to change. Even if that perfect measure is found, it cannot be used as a primary outcome if it is not widely recognized and viewed as the "gold standard" of measurement in the area.

This panel will examine how we can improve the accuracy of measurement through 1) improving measures already being used in clinical trials, 2) examining whether there are other measures that are not yet recognized as appropriate for clinical trial measurement which could provide improved measurement, 3) determining how to proceed when it is determined that a valid and reliable measure does not exist to assess a specific symptom, set of symptoms or disorder.

Learning Objectives

- Identify gaps in clinical trial measurements.
- Identify improved measurements to improve the gaps.

THE PATIENT-CENTERED OUTCOME GAP IN CNS CLINICAL TRIALS: PERSPECTIVES FROM A CARD-CARRYING PSYCHIATRIC HEALTH SERVICES RESEARCHER

Bradley Gaynes, University of North Carolina

Individual Abstract The design of CNS clinical trials requires carefully selecting outcomes to increase the likelihood of identifying a clinically meaningful signal that separates an experimental intervention from a control or standard treatment. Traditionally, these tools measure specific symptoms of psychiatric illness, such as depressive severity or psychotic symptomatology. Patient-centered outcomes -- which involve measures that are more directly meaningful to patients, such as side effects, functionality, and quality of life -- are challenging to measure and less frequently reported. However, these measures, identified as a national priority in the Affordable Care Act, are key to the development of evidence-based care and treatment guidelines and a necessity for psychiatric clinical trials research. This presentation will define patient-

centered outcomes and clarify their significance for psychiatric research; provide examples of gaps in the current CNS clinical trial literature; point out how those gaps hinder the translation of clinical trial data into evidence-based treatment guidelines; and encourage audience participation in a discussion of strategies to include more patient-reported outcomes in psychiatric clinical trials.

Learning Objectives

- To review the definition and importance of patient-centered outcomes in psychiatric clinical trials research.
- To identify examples of patient-centered outcome gaps in the psychiatric literature and how they hinder guideline development.
- To discuss feasible strategies for including more patient-centered outcomes in psychiatric clinical trials.

Literature References

- Jonas D. E., Mansfield A. J., Curtis P., Gilmore J. H., Watson L. C., Brode S., et al. (2012). Identifying priorities for patient-centered outcomes research for serious mental illness. Psychiatr Serv, 63(11), 1125-1130. doi: 10.1176/appi.ps.201100369
- Revicki D. A., Kleinman L., & Cella D. (2014). A history of health-related quality of life outcomes in psychiatry. Dialogues Clin Neurosci, 16(2), 127-135.
- Ahmed S., Berzon R. A., Revicki D. A., Lenderking W. R., Moinpour C. M., Basch E., et al. (2012). The use of patient-reported outcomes (PRO) within comparative effectiveness research: implications for clinical practice and health care policy. Med Care, 50(12), 1060-1070. doi: 10.1097/MLR.0b013e318268aaff

SINS OF THE FATHER: THE PANSS FOR THE NEXT 30 YEARS

Mark Opler, ProPhase, LLC

Individual Abstract The Positive and Negative Syndrome Scale (PANSS) has been a cornerstone of schizophrenia research for three decades and it has been central to major discoveries and developments in psychopharmacology. However, the limitations inherent in the scale are apparent. To drive the field forward, it is important to have a critical view, requiring a re-thinking of the way in which the PANSS is administered as well as the breadth and depth of the symptoms it focuses on. The planned revisions to the PANSS manual, tools for collecting and evaluating PANSS data, and the methods for training and maintaining inter-rater reliability are long overdue. Findings on psychometrics of the PANSS in different populations, performance of the PANSS in evaluating of novel mechanisms of action beyond "classic" second generation antipsychotics, and related items will be presented. A discussion of the data being assembled to drive the revisions to the scale will be presented, along with a protocol for a new North American normative study. Audience participation and input will be sought on the architecture and framework for revitalizing this venerable scale.

Learning Objectives

- To review current limitations, critiques, and challenges in the use of the PANSS in modern psychopharmacology research.
- To present and discuss the planned revisions and modifications to the PANSS.
- To obtain audience input and feedback on the revision and modernization process.

Literature References

- A new Integrated Negative Symptom structure of the Positive and Negative Syndrome Scale (PANSS) in schizophrenia using item response analysis. Khan A, Lindenmayer JP, Opler M, Yavorsky C, Rothman B, Lucic L. Schizophr Res. 2013 Oct;150(1):185-96. doi: 10.1016/j.schres.2013.07.007.
- Converting positive and negative symptom scores between PANSS and SAPS/SANS. van Erp TG, Preda A, Nguyen D, Faziola L, Turner J, Bustillo J, Belger A, Lim KO, McEwen S, Voyvodic J, Mathalon DH, Ford J, Potkin SG, Fbirn. Schizophr Res. 2014 Jan;152(1):289-94. doi: 10.1016/j.schres.2013.11.013.
- Assessing the sources of unreliability (rater, subject, time-point) in a failed clinical trial using items of the Positive and Negative Syndrome Scale (PANSS). Khan A, Yavorsky WC, Liechti S, DiClemente G, Rothman B, Opler M, DeFries A, Jovic S. J Clin Psychopharmacol. 2013 Feb;33(1):109-17. doi: 10.1097/JCP.0b13e3182776ebe.

MEASURES OF COGNITION IN CLINICAL TRIALS: ARE WE BEING SENSITIVE ENOUGH?

Chris Brady, inVentiv Health

Individual Abstract Clinical trials have advanced in numerous ways including the expanded use of biomarkers, molecule precision in targeting symptoms and the explosion of new technologies for collecting and sharing data. While these things have advanced, much of what we have been doing to assess cognition in clinical trials has not changed.

We continue to use psychometric measurements initially created for alternate purposes and we tend to use these measurements in non-standard ways. The MMSE was created as a quick tool to categorize individuals as impaired or not, and there are very few Alzheimer's disease or Parkinson's disease studies not using it for assessing inclusion and at times a measurement of change. Similarly, while we often see sub-tests of the Wechsler Scales included in clinical trials, the individual doing the administration would not meet the established training and experience by the developers.

Efforts have been made to develop standard measures and to improve measurements in current use. The National Institute of Mental Health's Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiativeties has made great strides in development of a consensus battery for measuring cognition in schizophrenia for clinical trials. Similarly the Alzheimer's disease Cooperative Study (ADCS) has developed and is working on improvement for the Alzheimer's disease Assessment Scale - Cognitive Subscale (ADAS-cog), a measure of cognitive performance, which is currently seen as the "Gold Standard" for assessing change in Alzheimer's disease trials. Similar efforts had been put toward development of specific cognitive measures for various indications (e.g. Neuropsychological Test Battery-NTB and SCales for Outcomes in PArkinson's disease-Cognition - SCOPA-cog).

Unfortunately, despite these efforts, the industry is continuing to have difficulty in demonstrating a statistically significant change in cognition across numerous indications. While it certainly could be that we have yet to find investigational products that can improve cognition, it is also possible that we are not using sensitive enough measurements in a standardized way. Ongoing evaluations of the assessments utilized in clinical trials will be discussed along with potential further improvements in this area.

Learning Objectives

- Increase awareness of the current limitations in cognitive measures used in clinical trials.
- Identify ways to improve measurement of cognition in clinical trials.

Literature References

- Cano, S.J., Posner, H. B, et al (2010) The ADAS-cog in Alzheimer's disease clinical trials: psychometric evaluation of the sum and its parts. Journal of Neurology, Neurosurgery & Psychiatry, 29 (Sep), pp. 1363– 368.
- Green, M.F., Nurehterlein, K.H, et al (2004). Approaching a consensus cognitive battery for clinical trials in schizophrenia: The NIMH-MATRICS conference to select cognitive domains and test criteria. Biological Psychiatry, 56 (5), pp.301–307.

CLINICAL STAGING: A NEW APPROACH TO BIPOLAR DISORDER

Flavio Kapczinski, The University of Texas Health Science Center At Houston

Overall Abstract Clinical staging model is emerging as a novel and useful paradigm to study phasic nature of progression of psychiatric disorders such as bipolar disorder (BD). BD illness progression has been associated with a higher number of mood episodes and hospitalizations, reduced interepisode intervals, poor response to treatment, and more severe cognitive and functional impairments (Berk et al., 2011). Recurrent episodes influence the outcome of BD by increasing vulnerability of patients to subsequent episodes and reducing the treatment response. Staging model of BD could help clinicians understand the mechanisms underlying the course of the illness and guide prognosis and therapy. Neurocognitive studies reported that BD patients at late stages were significantly more impaired than those at early stage of this illness in distinct domains of functioning. Individuals with BD often experience persistent neurocognitive deficits and poor psychosocial functioning even when they are euthymic. Also, neurocognitive impairment has been related to a worse clinical course and poor psychosocial functioning. Furthermore, peripheral biomarkers like inflammatory markers, DAMPs (damage-associate molecular patterns,-cell free (ccf) DNA, heat shock proteins HSP70, HSP90, and HSP60, and cytochrome C), neurotrophic factor, oxidative stress, mitochondrial dysfunction and apoptosis are pertinent to the theme of staging as they are conceptualized as mediators of allostasis and their demonstration in different stages is one of the fundamental hypotheses of neuroprogression (Fries et al., 2012; Pfaffenseller et al., 2014). In addition, alterations in brain structures have been widely reported in BD. Neuroimaging data suggest incremental volume loss and structural and functional networks could be differently affected in each illness stage. These patients also have a declining likelihood of response to pharmacological and psychosocial treatments. It further supports the concept of neuroprotection, in that a diversity of agents has putative effects against these targets. Prompt treatment may be potentially neuroprotective and attenuate the neurostructural and neurocognitive changes that emerge with chronicity. Staging highlights the need for interventions at a service delivery level and implementing treatments at the earliest stage of illness possible. Longitudinal and clinical trials may help to clarify the potential use of staging systems in BD.

Learning Objectives

- Describe the summary of biomarkers that suggests progression of bipolar disorder.
- Highlight recent advances in cognitive and biomarkers that suggest neuroprogression in BD.

Literature References:

- Berk M, Brnabic A, Dodd S, et al. Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. Bipolar Disord 2011; 13: 87–98.
- Fries GR, Pfaffenseller B, Stertz L, Paz AV, Dargél AA, Kunz M, Kapczinski F. Staging and neuroprogression in bipolar disorder. Curr Psychiatry Rep 2012; 14: 667-75.
- Pfaffenseller B, Wollenhaupt-Aguiar B, Fries GR, Colpo GD, Burque RK, Bristot G, Ferrari P, Ceresér KM, Rosa AR, Klamt F, Kapczinski F. Impaired endoplasmic reticulum stress 136 response in bipolar disorder: cellular evidence of illness progression. Int J Neuropsychopharmacol. 2014; 17:1453-63.

COGNITIVE IMPAIRMENT AS A MARKER OF LATE-STAGE LATE-LIFE DEPRESSION

Breno Satler Diniz, Department of Mental Health, Faculty of Medicine, Federal University of Minas Gerais

Individual Abstract Late-life depression (LLD) is a common psychiatric condition in the elderly. It has a heterogeneous clinical presentation and is an independent risk factor for functional impairment, dementia, and death. Strategies to stage patients with LLD can help to reduce the clinical heterogeneity and improve prediction models for this disorder. Recent studies showed that the identification of mild cognitive impairment (MCI) in LLD could identify a subgroup of patients that are at increased risk for dementia and death. In addition, we found that these subjects have a distinct profile of abnormalities in different neurobiological cascades. In a study including a total of 166 subjects (130 with LLD and 36 healthy controls), we demonstrated that subjects with LLD and MCI presented with reduced neurotrophic support and showed a faster decline in plasma BDNF levels over two years of follow-up compared to subjects with LLD and normal cognitive performance and healthy controls (estimated difference = 6.04 (se = 2.06) , p 0.004)1. In a recent study using a multimodal biomarkers analysis approach (plasma proteomics, structural neuroimaging and in vivo β-amyloid imaging), including 36 subjects with LLD and MCI and 44 subjects with LLD and no cognitive disorder, we found that 24 proteins were abnormally expressed in LLD + MCI. Moreover, these subjects had higher cerebrovascular disease when compared to those with LLD and no cognitive disorder (t=2.49, p=0.015). Pathway enrichment analysis showed that the proteins abnormally expressed in LLD + MCI were related to several biological pathways and molecular processes, in particular abnormal immune and inflammatory response, increased oxidative stress, endoplasmic reticulum stress, reduced cell survival, and increased apoptosis markers2. Such changes are similar to those observed in older adults with neurodegenerative disorders, such as Alzheimer's disease. Thus, we propose that the presence of cognitive impairment in older adults with LLD may represent a later stage in the evolution of this disorder and indicate more severe brain disorder. These subjects are at higher risk of negative health outcomes, in particular of functional impairment, dementia and death. The correct identification of these subjects can help to select interventions aiming the treatment of cognitive impairment in LLD and the prevention of the negative outcomes associated with this condition.

Learning Objectives

- Cognitive impairment in late-life depression (LLD) is associated with distinct neurobiological abnormalities.
- Cognitive impairment can represent a late-stage marker of LLD, indicating a more severe brain dysfunction in these individuals.

Literature References

- Diniz BS, Reynolds CF 3rd, Begley A, Dew MA, Anderson SJ, Lotrich F, et al. Brain-derived neurotrophic factor levels in late-life depression and comorbid mild cognitive impairment: a longitudinal study. J Psychiatr Res. 2014 Feb;49:96-101. doi: 10.1016/j.jpsychires.2013.11.004.
- Diniz BS, Sibille E, Ding Y, Tseng G, Aizenstein HJ, Lotrich F, et al. Plasma biosignature and brain pathology related to persistent cognitive impairment in late-life depression. Mol Psychiatry. 2014 Aug 5. doi: 10.1038/mp.2014.76. [Epub ahead of print]

NEUROIMAGING EVIDENCE OF PROGRESSION OF BIPOLAR DISORDER

Sudhakar Selvaraj, The University of Texas Health Science Center at Houston

Individual Abstract Bipolar Disorder (BD) is a common and major health problem in the US and worldwide (1). The lifetime prevalence between 1-3 % and the peak age of onset is between 15 and 25. Due to its recurrence and chronicity of the illness, BD is associated with significant decline in cognitive and psychosocial functioning. The underlying neurobiology of BD is less known. This presentation will summarize literature findings regarding neuroimaging and progression in BD. Several magnetic resonance imaging (MRI) studies have reported alteration in brain structure in BD, including increased lateral ventricular size, increased white matter hyper intensities and grey matter volume reductions in the prefrontal and temporal cortices and anterior cingulate cortex (ACC), key prefronto-limbic areas in mood dysregulation. Brain volume reductions are more pronounced in later stages of BD and those with longer duration of illness. The cytoarchitecture of the MRI volume changes is unclear but postmortem studies suggest reduced neuronal and glial densities and/or morphology in BD. Neuroinflammation, and oxidative stress have been implicated as potential pathophysiological mechanisms underlying progressive brain volume loss observed in BD. Recently, a Positron Emission Tomography (PET) study showed significantly increased TSPO (an inflammatory marker) binding in hippocampus of euthymic and medicated bipolar patients with average >5 mood episodes (2). The neurocognitive, neuroanatomical, and functional abnormalities may possibly be due to the cumulative adverse effect of repeated mood episodes. In summary, the above evidence suggests staging of BD should include brain imaging markers along with clinical findings.

Learning Objectives

- Describe the summary of brain imaging evidence that suggests progression of Bipolar disorder.
- Highlight recent advances in functional imaging that suggest neuroprogression in BD.

Literature References

- Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, Kessler RC. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry. 2007;64:543-552.
- Haarman BC, Riemersma-Van der Lek RF, de Groot JC, Ruhé HG, Klein HC, Zandstra TE, Burger H, Schoevers RA, de Vries EF, Drexhage HA, Nolen WA, Doorduin J. Neuroinflammation in bipolar disorder - A [(11)C]-(R)-PK11195 positron emission tomography study. Brain Behav Immun. 2014.

NEUROPROGRESSION AND BIPOLAR DISORDERS: BRAIN IMAGING AND NEUROCOGNITIVE STUDIES

Jair Soares, University of Texas School of Medicine at Houston

Individual Abstract An increasing body of literature has suggested that bipolar disorders are progressive and carry substantial brain involvement, which generally worsens with increased number of episodes and longer illness duration. This presentation will review available evidence from brain imaging and neurocognitive studies that suggests that bipolar disorders involve gradual progression of brain abnormalities, which may underlie substantial functional impairment and disability present in these patients. This emphasizes the need for clinical approaches that will focus on different stages of the illness, as more appropriate interventions to help our patients improve symptomatically and recover as much functionality as their disease status will allow them.

Learning Objectives

- Learn about current neuroimaging evidence that documents fronto-limbic abnormalities in patients with bipolar disorder.
- Learn about current neurocognitive studies that document cognitive abnormalities in patients with bipolar disorder.

Literature References

- Inflammatory mediators of cognitive impairment in bipolar disorder. Bauer IE, Pascoe MC, Wollenhaupt-Aguiar B, Kapczinski F, Soares JC. J Psychiatr Res. 2014 Sep;56:18-27. doi: 10.1016/j.jpsychires.2014.04.017. Epub 2014 May 2. PMID: 24862657 [PubMed - in process]
- Structural magnetic resonance imaging in bipolar disorder: an international collaborative mega-analysis of individual adult patient data. Hallahan B, Newell J, Soares JC, Brambilla P, Strakowski SM, Fleck DE, Kieseppä T, Altshuler LL, Fornito A, Malhi GS, McIntosh AM, Yurgelun-Todd DA, Labar KS, Sharma V, MacQueen GM, Murray RM, McDonald C. Biol Psychiatry. 2011 Feb 15;69(4):326-35. doi: 10.1016/j.biopsych.2010.08.029. Epub 2010 Oct 27. PMID: 21030008 [PubMed - indexed for MEDLINE]

10:15 a.m. - 11:45 a.m.
REGULATORY WRAP-UP PLENARY

Chair: Maurizio Fava, Massachusetts General Hospital

Speakers: Tiffany Farchione, Food and Drug Administration
Luca Pani, AIFA Italian Medicines Agency