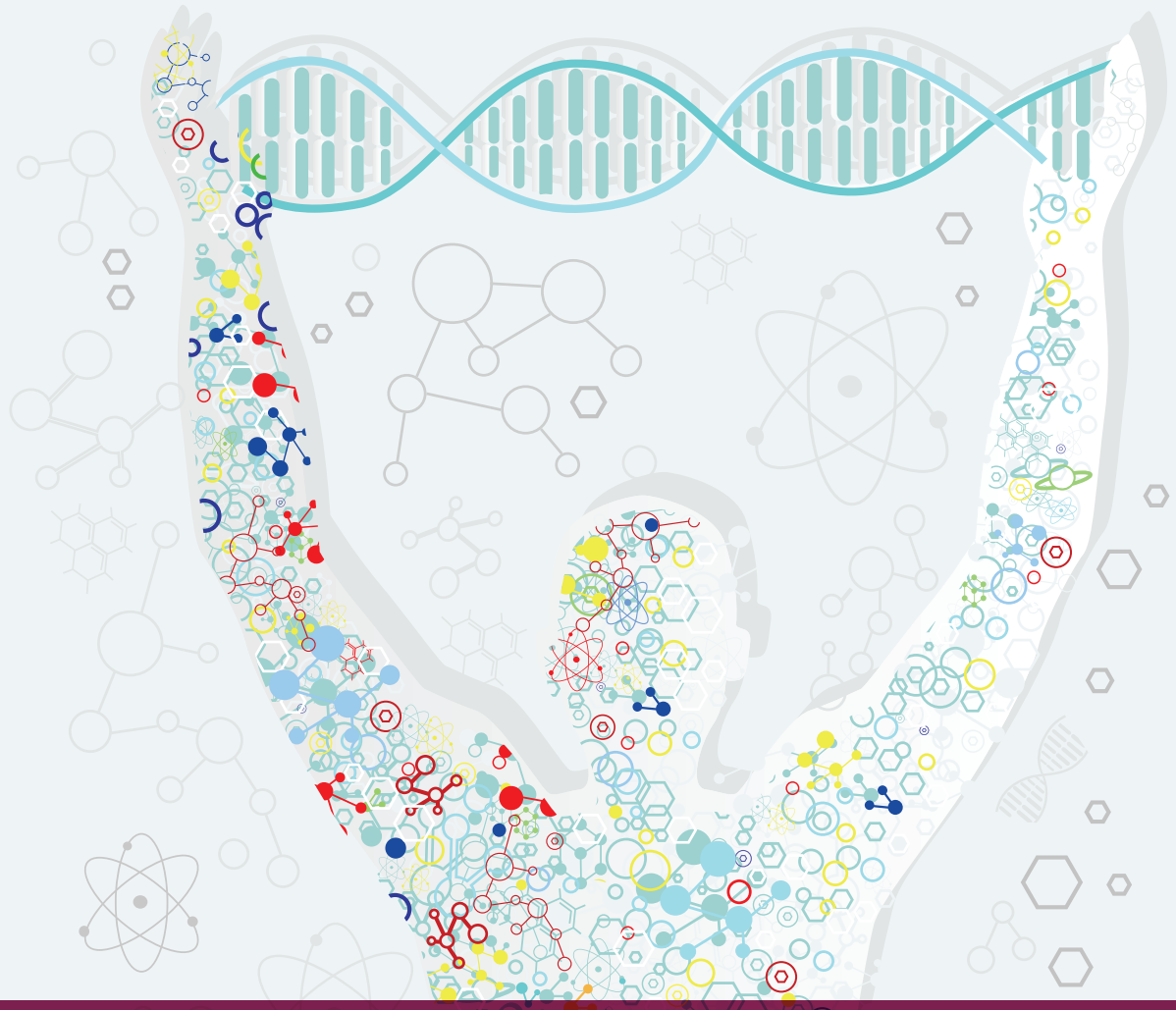
MAY 28-31, 2019 | FAIRMONT SCOTTSDALE PRINCESS



ASCP 2019 Annual Meeting

Innovations in Personalized Medicine: From Biomarkers to Patient-Centered Care

ASCP
American Society of Clinical Psychopharmacology

www.ASCPMeeting.org

ORAL ABSTRACT BOOK

Tuesday, May 28, 2019

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

NEW AND HOPEFULLY IMPROVED! NOVEL DELIVERY SYSTEMS OF ANTIPSYCHOTIC MEDICATIONS FOR THE TREATMENT OF SCHIZOPHRENIA*

Leslie Citrome, New York Medical College

Overall Abstract: Antipsychotic medications have traditionally been administered by mouth or by intramuscular injection. Advances in technology has made possible the development of transdermal delivery systems ("patches"), polymers amenable for subcutaneous placement, and different particle sizes for products intended to be injected into the muscle. This enables more novel approaches for medication administration that may be of high value to patients and their clinicians.

Learning Objectives:

1. Review new formulations of antipsychotic medications, including delivery through the skin, directly under the skin, and in the muscle.
2. Review how the pharmacokinetic profile of antipsychotic medications can be altered using different technologies.

PATCH ME UP: TRANSDERMAL DELIVERY SYSTEMS

Leslie Citrome, New York Medical College

Individual Abstract: Transdermal delivery is an alternative to oral routes of drug administration and has made considerable contributions to the treatment of various medical diseases. With the advent of new transdermal delivery technologies, higher numbers of medications are being approved for use as transdermal formulations. This route of administration has several innate advantages that have the potential to benefit various patient populations, including those with central nervous system disorders. The presentation briefly outlines the history of transdermal medications, discusses the advantages and disadvantages of transdermal formulations, and examines the challenges and opportunities present for the use of transdermal treatments in psychiatry. Patients with psychiatric illnesses have many unmet needs that may be filled through the benefits gained from transdermal treatments, such as reduced dosing frequency, effective control of medication plasma concentrations, improved tolerability, ability to check compliance visually, and avoidance of first-pass hepatic metabolism. Established transdermal treatments for various psychiatric diseases are discussed followed by an introduction to therapies that are being developed as the first patch formulations for the treatment of schizophrenia.

Learning Objectives:

1. To be aware of the advantages and disadvantages of transdermal drug delivery systems.
2. To be aware of recent work in the development of an antipsychotic medication "patch".

Literature References:

1. Pastore MN, Kalia YN, Horstmann M, Roberts MS. Transdermal patches: history, development and pharmacology. Br J Pharmacol. 2015;172(9):2179-2209.
2. Citrome L, Walling D, Zeni C, Komaroff M, Park A.Efficacy and safety of an asenapine transdermal patch (asenapine transdermal system, HP-3070) in the treatment of adults with schizophrenia: a Phase 3 randomized, double-blind, placebo-controlled, 6-week,

inpatient study. Poster Abstract, 57th Annual Meeting of the American College of Neuropsychopharmacology, December 9-13, 2018, Hollywood, California.

I'VE GOT YOU UNDER MY SKIN: SUBCUTANEOUS RISPERIDONE LONG-ACTING INJECTABLE

John Lauriello, University of Missouri

Individual Abstract: Historically, long acting antipsychotics have only been available in an intramuscular formulation. While this formulation has been effective, it poses some potential problems including unintended injection into the vascular system and for some antipsychotics painful space occupying carriers in the musculature. In addition, the intramuscular needle may be too short for large patients (thus missing the muscle) or too long (and painful) for very thin patients.

Subcutaneous injections have a long tradition in other fields of medicine including for anti-coagulation and diabetes control. The FDA approval of a once monthly subcutaneous risperidone injection provides a new way of administrating injectable antipsychotics (a potential advantage over every two-week risperidone microspheres). The potential success of this formulation may usher interest in developing long acting antipsychotics not currently available or in existing long acting antipsychotics where the formulation is not readily used.

In this presentation we will discuss the difference between intramuscular injectable antipsychotics and the new subcutaneous risperidone formulation. Data supporting the FDA approval will be discussed as well as dosage and administration information. Other subcutaneous long acting injectable antipsychotics in the pipeline will also be touched on.

Learning Objectives:

1. Understand the difference between long acting intramuscular and long acting subcutaneous injectable antipsychotics.
2. Understand the specifics of the new long acting once monthly subcutaneous risperidone injection including the FDA approval data and dosage and administration information.

Literature References:

1. Correll CU, Citrome L, Haddad PM, Lauriello J, Olfson M, Calloway SM, Kane JM.: The use of long-acting injectable antipsychotics in schizophrenia: Evaluating the evidence. J Clin Psychiatry. 2016;77(suppl 3):1-24
2. Citrome L: Sustained-release risperidone via subcutaneous injection: A systematic review of RBP-7000 (Perseris TM) for the treatment of schizophrenia. Clin Schizophr Rela Psychoses 2018 12(3): 130-141

PARTICLE SIZE MATTERS: DEVELOPING A 1-DAY INITIATION REGIMEN FOR ARIPIPRAZOLE LAUROXIL

Peter Weiden, Alkermes, Inc.

Individual Abstract: Background: Long-acting formulations provide consistent therapeutic plasma antipsychotic concentrations without having to rely on the uncertainties of following a daily oral medication regimen. All long-acting injectable (LAI) antipsychotics release drug gradually over weeks to months. The release of drug and time intervals between LAI treatments is impacted by the dissolution rate of the drug, with slower dissolution allowing for relatively longer intervals between administrations. However, one of the challenges of slow dissolution is that it translates into a delay in reaching clinically relevant plasma concentrations with the first LAI injection.

Historically, two strategies have been used for atypical LAIs to address this issue: 1) administering a supplemental oral antipsychotic for some time after the first LAI dose, or 2)

giving a higher dose of the LAI up front (i.e., a "loading dose") to reduce or eliminate the need for oral supplementation. This presentation describes a third strategy for starting an LAI antipsychotic that was developed to reduce the time needed for oral supplementation when starting aripiprazole lauroxil (AL) treatment, from 21 days to a single day by concomitantly administering a rapid dissolution formulation of AL (ALNCD).

Methods: The slow dissolution properties of AL preclude a loading dose approach (e.g., the appearance of aripiprazole in systemic circulation starts 5-6 days after the first AL injection) prompted investigation into alternative approaches to reduce the 21 days of oral aripiprazole supplementation required when initiating AL treatment. Drug dissolution is influenced by the particle size of the drug placed into suspension. Therefore, a strategy was taken to reformulate AL into another drug product with reduced particle size, leading to faster dissolution. This AL reformulation, known as AL NanoCrystal Dispersion (ALNCD), reduced the particle diameter from micrometer-sized particles to nanometer-sized particles. As a result of this reformulation, ALNCD has a faster dissolution and shorter mean terminal elimination half-life than AL (15-18 days vs. 54-57 days, respectively). The pharmacokinetics and safety of ALNCD + AL + one oral dose of aripiprazole (30 mg) as an initiation regimen were evaluated in comparison to the original initiation regimen of AL + 21 days of oral aripiprazole (15 mg/d).

Results: The pharmacokinetics and safety profile of the 1-day initiation regimen were comparable to those of the 21-day oral aripiprazole initiation regimen onto AL. Each component of the 1-day regimen delivered aripiprazole to the systemic circulation at different time periods.

Conclusions: Through AL reformulation efforts aimed at decreasing the particle size of drug in suspension resulted in the development of ALNCD. When administered in conjunction with one 30 mg dose of oral aripiprazole, ALNCD provides a new initiation regimen for AL, which is an alternative starting regimen from the original, which required 21 days of oral aripiprazole supplementation.

Learning Objectives:

1. Review the relationship between formulation characteristics and pharmacokinetic properties of long-acting antipsychotics.
2. Discuss the rationale for a reformulation of the drug, aripiprazole lauroxil, that was developed as part of a 1-day initiation regimen.

Literature References:

1. Hard ML, Wehr AY, Du Y, Weiden PJ, Walling D1, von Moltke L. Pharmacokinetic Evaluation of a 1-Day Treatment Initiation Option for Starting Long-Acting Aripiprazole Lauroxil for Schizophrenia. J Clin Psychopharmacol. 2018 Oct;38(5):435-441.
2. Hard ML, Wehr AY, Sadler BM, Mills RJ, von Moltke L. Population Pharmacokinetic Analysis and Model-Based Simulations of Aripiprazole for a 1-Day Initiation Regimen for the Long-Acting Antipsychotic Aripiprazole Lauroxil. Eur J Drug Metab Pharmacokinet. 2018 Aug;43(4):461-469.

LEVERAGING PRIOR EXPERIENCE TO FACILITATE PEDIATRIC CLINICAL DEVELOPMENT FOR PSYCHIATRY PRODUCTS*

Hao Zhu, U.S. Food and Drug Administration

Overall Abstract: There is an urgent need to facilitate clinical development of drugs for pediatric use. The average delay between approval of a drug with an indication for adults and approval of that same drug's pediatric indication is approximately 5 years. As the result, there is a period of time in which a drug is available and, often, being prescribed to pediatric patients

with little guidance on appropriate dosing, expected rates of adverse reactions, or even whether the drug is effective for pediatric patients. The development of psychiatry products shares the same issue.

The delay to pediatric labeling can be largely attributed to the time needed for clinical development programs in pediatric patients. In typical drug development programs, sponsors do not initiate the pediatric clinical trials until the drug is shown to be safe and effective in adults. Enrolling patients into pediatric efficacy and safety trials can be challenging. For psychiatric illnesses such as bipolar disorder or schizophrenia, the prevalence rate is lower in the pediatric population as compared to adults. It may take a long time to enroll enough pediatric patients to ensure sufficient statistical power.

In recent years, the Division of Psychiatry Products (DPP), working with other disciplines at the Food and Drug Administration (FDA), has taken the initiative to facilitate pediatric development of psychiatry products. In this panel session, we will share the Division's latest scientific findings based on the data collected from multiple New Drug Application (NDA) submissions. In addition, we will discuss the Division's new recent change in policy allowing for streamlined pediatric development of psychiatry products.

Dr. Lynne Yao will provide an overview of the challenges in pediatric development programs across various indications. She will share the Agency's recent efforts to improve the efficiency of clinical development programs in pediatric patients. She will describe policies intended to encourage sponsors to begin their pediatric programs earlier in drug development. In addition, she will share the general thinking on when extrapolation strategy can be considered in a pediatric development program.

Dr. Tiffany Farchione will share DPP's most recent efforts to enhance pediatric clinical development of psychiatry products. These efforts include active scientific research projects to understand the similarities and differences in response to drugs between adult and pediatric patients, and resultant policy development. Specifically, she will share information relevant to pediatric development of various psychiatry products and discuss guidance's under development for CNS stimulants, drugs for the treatment of insomnia, and antidepressants.

Dr. Shamir Kalaria will present his scientific research project aiming to compare the similarity in disease progression and patient response (efficacy and safety) in pediatric and adult patients with schizophrenia following antipsychotic treatment. Furthermore, he will show how the research findings have informed policy to guide clinical development programs of various drugs intended to treat schizophrenia.

Dr. Yaning Wang will provide an update on disease modeling and exposure-response modeling in pediatric and adult patients with bipolar disorder receiving either monotherapy or adjunctive therapy. Based on the findings, the potential policy change in pediatric bipolar programs will be discussed.

Learning Objectives:

1. To share the DPP's current efforts to streamline pediatric clinical development programs for psychiatry products.
2. To seek input on further improvements in pediatric clinical development programs for psychiatry products.

AN OVERVIEW OF FDA'S EFFORT IN IMPROVING DRUG DEVELOPMENT FOR PEDIATRIC USE

Lynne Yao, U.S. Food and Drug Administration

Individual Abstract: There is an urgent need to facilitate clinical development of drugs for pediatric use. The average delay between approval of a drug with an indication for adults and approval of the same drug's pediatric indication can be as long as 8-9 years. As the result, the

newest treatment option for adults may only be available for pediatric patients as "off-label use". Health providers may have to prescribe the drug to pediatric patients without full knowledge of appropriate dosing, anticipated treatment effect, or risks for different adverse events in pediatric patients. The issue is common across various drugs regulated by the U.S. Food and Drug Administration (FDA).

The time needed for pediatric clinical development programs appear to be the main reason for the delay of drug approval in pediatric patients. A standard pediatric program if often not initiated before the drug is approved in adults. Pediatric patient enrollment may be challenging because disease prevalence may be significantly different between adult and pediatric patients. For diseases less prevalent in pediatric patients, it may take many years to enroll adequate number of pediatric patients to ensure statistical power.

To streamline the pediatric development program of new drugs, FDA has taken several initiatives. For example, efforts have been put to optimize the clinical trial data needed in a pediatric development program. In recent years, the agency has even attempted to approve pediatric indications based on pediatric extrapolation. The approval of the indication in pediatric patients can be based, in certain cases, on similarity in exposure between adult and pediatric patients.

In this presentation, we would like to share the main challenges and opportunities in pediatric development programs. Based on the recent scientific findings, some innovative approaches have been taken to facilitate the development of drugs for pediatric use. Policies have been established to improve the efficiency of pediatric clinical development programs. Some experiences obtained from the other pediatric development programs may be applied to enhance the development of psychiatry products for pediatric use.

Learning Objectives:

1. Review important drug development laws related to pediatric therapeutics development.
2. Review pediatric extrapolation as it relates to development of drugs to treat children with psychiatric disorders.

Literature References:

1. Green DJ, Burnham JM, Schuette P, Liu XI, Maas BM, Yao L, McCune SK, Chen J, van den Anker JN, Burckart GJ., Primary Endpoints in Pediatric Efficacy Trials Submitted to the US FDA., J Clin Pharmacol. 2018 Jul;58(7):885-890. doi: 10.1002/jcph.1109. Epub 2018 Apr 17
2. Mulugeta YL, Zajicek A, Barrett J, Sachs HC, McCune S, Sinha V, Yao L, Development of Drug Therapies for Newborns and Children: The Scientific and Regulatory Imperatives, Pediatr Clin North Am. 2017 Dec; 64(6): 1185-1196

AN UPDATE ON THE DIVISION OF PSYCHIATRY PRODUCTS' (DPP'S) INITIATIVES TO FACILITATE DEVELOPMENT OF DRUGS FOR PEDIATRIC USE

Tiffany Farchione, US Food and Drug Administration

Individual Abstract: In recent years, the Division of Psychiatry Products (DPP) at the U.S. Food and Drug Administration (FDA) has undertaken several initiatives to facilitate development of psychiatry products for pediatric use. This presentation will provide an overview of the Division's current efforts, including scientific research projects, policy development, and new guidance preparation.

DPP, working together with multiple disciplines at FDA, has launched several research projects. The projects intend to compare disease similarity and drug response (i.e., efficacy) between pediatric and adult patients using clinical trial data submitted as part of New Drug

Applications (NDAs). We also compared the incidences of adverse events between adult and pediatric patients receiving the same treatment. We are also making efforts to identify reasons for the failure of several pediatric clinical trials of drugs approved in adults. Dr. Wang and Dr. Kalaria will provide the detailed findings in patients with bipolar disorder and with schizophrenia.

DPP plans to translate the scientific findings into new policies with the objective to streamline the pediatric clinical development programs for various psychiatry products. For example, the Division has encouraged the sponsors to enroll adolescent patients with schizophrenia into adult clinical trials, because the clinical responses in both placebo and drug treatment arms are similar between the adult and adolescent patients. In this way, the efficacy and safety information can be obtained to support appropriate pediatric dosing by the time the drug is available for adults.

Beyond schizophrenia, policies are under development for new drugs treating Attention Deficit Hyperactivity Disorder (ADHD). Based on the tight relationship between concentration and treatment response, we have determined that, for some pharmaceutical alternative products of methylphenidate or amphetamine, it may be appropriate to extrapolate efficacy findings from pediatric patients 6 to12 years of age to adolescents and adults if the pharmacokinetic profiles in these patient populations are similar. These policy changes will be reflected in the new Agency guidance.

Learning Objectives:

1. Understand how the Division of Psychiatry Products is using existing data to explore the acceptability of pediatric extrapolation in novel contexts.
2. Describe the application of existing data to new policy and guidance.

Literature References:

1. Dunne J, Rodriguez WJ, Murphy D, et al. Extrapolation of adult data and other data in pediatric drug development programs. Pediatrics. 2011;128:1242–9
2. US Department of Health and Human Services. Guidance for industry: Attention Deficit Hyperactivity Disorder: Developing Stimulant Drugs for the Treatment. In preparation.

OPTIMIZING PEDIATRIC DRUG DEVELOPMENT FOR SCHIZOPHRENIA: FDA'S MODEL INFORMED APPROACH TO EXTRAPOLATE EFFICACY

Shamir Kalaria, University of Maryland School of Pharmacy

Individual Abstract: Objective: Drug development in pediatrics is typically challenged by disease heterogeneity, patient recruitment, high attrition, and ethical concerns regarding specific trial designs. Pathways to expediate pediatric drug development have been substantially explored over the last decade. Extrapolation based methods have been proposed by FDA since 1994, where knowledge from previous experience can be utilized to inform the need for additional information in the pediatric population. Currently, only six antipsychotics have been approved in adolescents. Quantitative relationships between antipsychotic exposure and clinical response (total PANSS scores) are relatively unexplored in adolescents as compared to adults. This analysis will provide an insight to FDA's justification on extrapolating efficacy from adults to adolescents with schizophrenia.

Methods: An adult and pediatric schizophrenia database was constructed using sponsor submitted applications to the U.S. Food and Drug Administration (FDA) and consisted of nine adult (N=17,778) and six adolescent (N=2,122) second generation antipsychotic programs. A nonlinear mixed effect modeling approach was utilized to develop disease-drug-trial models that predict longitudinal changes in PANSS scores in adult and adolescent patients. Similarity

of placebo and antipsychotic-specific exposure-response relationships were evaluated by simulating adolescent PANSS scores using adult based models. Clinical trial simulations were also explored to identify potential reasons for negative findings in two adolescent programs. Differences in major adverse effects were analyzed using FDA authored reviews and approved products labels.

Results: Placebo response was found to be similar between adults and adolescents across all acute schizophrenia trials. Similar exposure-response relationships were also observed between both populations. Parametric time to event analysis demonstrated that adult patients experienced a two-fold higher dropout rate as compared to adolescents. Inappropriate trial design and lack of statistical power were major reasons that led to negative findings in two adolescent programs. No new adverse events were found in adolescent trials and minor differences in sedation, metabolic changes, and extrapyramidal symptoms were present between adults and adolescents.

Conclusions: This analysis demonstrates that full extrapolation is possible to approve second generation antipsychotics that have already been approved for adult use without the need for a dedicated efficacy trial in adolescents. For drugs that have novel mechanisms of action, the FDA is considering including adolescent patients into adult pivotal trials. The results of this analysis will hopefully provide additional therapeutic options and expedite the availability of antipsychotics in the pediatric population.

Learning Objectives:

1. To appreciate how clinical trial modeling and simulations can assist in justifying disease and exposure-response similarity to ultimately support full extrapolation.
2. To share FDA's current thinking regarding full extrapolation of efficacy and the potential for including pediatric patients into adult efficacy and safety trials.

Literature References:

1. Mulugeta Y, Barrett JS, Nelson R, et al. Exposure matching for extrapolation of efficacy in drug development. J Clin Pharmacol. 2016;56:1326-34
2. Barrett JS, Bishai R, Bucci-Rechtweg C, et al. Challenges and opportunities in the development of medical therapies for pediatric populations and the role of extrapolation. Clin Pharmacol Ther. 2018;103:419-33

ARE WE THERE YET? EXPLORING THE OPPORTUNITY TO EXTRAPOLATE EFFICACY FROM ADULTS TO PEDIATRICS WITH BIPOLAR I DISORDER

Yaning Wang, Center for Drug Evaluation and Research, Food and Drug Administration

Individual Abstract: Background: Bipolar disorder is a lifelong psychiatric illness that is characterized by significant morbidity and mortality and is often progressive. While onset of bipolar disorder most commonly occurs in adolescence or early adulthood, 20% to 40% of adults with bipolar disorder report onset during childhood. Individuals with early onset bipolar I disorder experience a more chronic, severe, and recurrent course of the disease. Thus, earlier recognition, diagnosis, and treatment of this impairing disorder is of great importance. Considering that the use of antipsychotic treatment is the standard of care across the course of bipolar I disorder, there has been a growing need for additional safe and efficacious treatment options in the pediatric population. Over the past decade, FDA has been accepting alternative ways to expedite pediatric drug development programs by utilizing the extrapolation principle. Similarity of disease progression and exposure-response can be used to support full extrapolation of efficacy from adults to adolescents. This presentation will provide an insight on how modeling and simulation can assist in comparing disease and exposure-response profiles between adults and pediatric patients.

Methods: The FDA recently created the largest clinical trial database that included patient-level data from 7 adult and 6 pediatric sponsor submitted programs for the treatment of bipolar I disorder. The Young Mania Rating Scale (YMRS) was used as the primary efficacy variables in this analysis. Sponsor submitted population pharmacokinetic models were used to simulate exposures. Disease-drug-trial models were developed that captured the longitudinal placebo response, exposure-response relationship, and dropout rate in adults and adolescents. In order to assess similarity, the adult model was used to simulate pediatric predictions that were then compared to the true pediatric observations. Differences in baseline demographics, prior psychiatric history, and trial design were also investigated.
Results: Preliminary results indicate that placebo response profiles were similar in both populations. No difference in placebo response were observed in patients with manic and mixed features included in adult and adolescent trials. Predictors for dropout included trial location, baseline severity, and symptomology improvement. Similar exposure ranges indicate that the reported adult dose ranges are also effective in the pediatric populations. Exposure-response analyses from three studied drug programs indicate similar treatment effect sizes and IC50 values.
Conclusion: Further analysis is currently undergoing to validate findings in other drug programs that have collected adult and adolescent information. If the current findings are upheld, a potential path to fully extrapolate efficacy from adults to pediatric patients can be considered.

Learning Objectives:

1. To compare placebo and exposure-response profiles between adults and pediatric patients with bipolar I disorder.
2. To share FDA's current thinking regarding full extrapolation of efficacy and the potential for including pediatric patients into adult efficacy and safety trials.

Literature References:

1. Sun W, Laughren TP, Zhu H, et al. Development of a placebo effect model combined with a dropout model for bipolar disorder. J Pharmacokinet Pharmacodyn. 2013 Jun;40(3):359-68.
2. Barrett JS, Bishai R, Bucci-Rechtweg C, et al. Challenges and opportunities in the development of medical therapies for pediatric populations and the role of extrapolation. Clin Pharmacol Ther. 2018;103:419-33

TREATMENT-RESISTANT MOOD DISORDERS ACROSS THE LIFESPAN: NOVEL THERAPEUTICS ON THE HORIZON*

Bashkim Kadriu, National Institute of Mental Health

Overall Abstract: A large proportion of patients with major depressive disorder (MDD) fail to respond to multiple levels of monoaminergic based treatments and augmentation strategies. Moreover, these therapies are often plagued by delayed therapeutic onset, a process that substantially prolongs patients' recovery and remission. Roughly a third of depressed subjects undergo several lines of therapy and are categorized as having treatment-resistant depression (TRD), which is highly associated with suicidality, significant individual and societal burden, and long-lasting functional impairment. Thus, there is an urgent need for novel and rapid-acting antidepressant therapies, as well as more personalized approaches for patients with TRD. Of the novel pharmacotherapeutic strategies seeking to rapidly alleviate depressive symptoms, glutamatergic modulators such as ketamine have shown rapid and, after repetitive applications, sustained antidepressant efficacy in adults with TRD. Noninvasive brain stimulation is an alternative treatment approach with well-established efficacy in this population. This

symposium will explore strategies in current and novel pharmacological and non-pharmacological approaches for treatment of TRD in adults and adolescents, identification of biomarkers of treatment response, and technological advances in neuromodulation. Dr. Christoph Kraus (Medical University of Vienna) will present data from a 7T MRI antidepressant treatment study and discuss predictability of response and remission. Dr. Jennifer Dwyer (Yale) will present a randomized midazolam-controlled trial of ketamine in adolescents with TRD and discuss these results in the context of adolescent glutamate system development. Dr. Bashkim Kadriu (NIMH) will discuss data from a randomized controlled trial assessing ketamine's effects with a focus on developing biomarkers of immune and stress systems in adults with unipolar or bipolar TRD. Dr. Zhi-De Deng (NIMH) will present technological innovations in brain stimulation, including the development of a novel form of seizure therapy, which combines state-of-the-art computational models to individualize electrical current dosage and multielectrode targeting.

Learning Objectives:

1. Understand how ketamine, a prototypic glutamatergic modulator, impacts depressive symptoms in adults and adolescents with treatment-resistant depression, and appreciate the potential role of neuroimmune and stress pathways in therapeutic efficacy.
2. Appreciate how novel seizure therapy approaches and state-of-the-art computational models can individualize treatment and improve the efficacy and side-effect profiles of ECT-based therapies.

PREDICTION OF ANTIDEPRESSANT TREATMENT OUTCOMES WITH ULTRA-HIGH FIELD MAGNETIC RESONANCE IMAGING

Christoph Kraus, Medical University of Vienna

Individual Abstract: Introduction: Structural and functional magnetic resonance imaging (sMRI/fMRI) has successfully discerned neuroanatomical substrates of major depressive disorder (MDD). In addition, assessment and prediction of treatment response with high-field (3T) fMRI yielded anterior cingulate, frontal and amygdalar activity as candidates for response prediction. However, previous studies did not yield sensitivities and specificities high enough to translate fMRI-findings into clinical settings (1, 2). Ultra-high field (7T) fMRI exhibits higher a special resolution and increased BOLD-signal strengths, potentially leading to advantages in antidepressant response prediction (3). We hence conducted a 7T antidepressant fMRI study and aimed to predict response and remission before treatment (at MRI-1).

Methods: We conducted a longitudinal, open-label, flexible-dose antidepressant treatment study with first line treatments (escitalopram-max. 20 mg) and an option to switch to second-line venlafaxine (max. 150 mg) upon non-response after 6 or 8 week-long treatment. 7T structural (MP2RAGE, 32-channel head coil, TR/TE=4060/3.02 ms, voxel x/y/z = 0.74 × 0.68 × 0.68 mm) and functional (multiband, TR/TE=1400/23 ms, voxel x/y/z = 1.5 × 1.5 × 1.0 mm, multiple paradigms) MRI was performed twice; 1 pretreatment scan and another after 12 weeks treating acute patients. In total 29 acute depressed subjects with MDD and as controls 39 stable remitted subjects and 38 healthies finished the protocol. In an electrical painful stimulation paradigm, we modelled 'dynamic response' to antidepressant treatment with a sigmoid function and compared pretreatment with post-treatment with a linear regression analysis. Moreover, we compared baseline and posttreatment hippocampal subfield volumes with a repeated measures ANOVA.

Results: In acute depressed patients (n=26) we found pretreatment elevated activity in the right temporoparietal junction significantly predicting remitter from non-remitter (t=4.1, FWE p=0.005). This cluster had an accuracy of 58%, sensitivity of 41.6% and specificity of 71.4%. Difference between fMRI-1 and fMRI-2 (i.e. treatment effects) between remitter and non-

remitter were associated with significantly increased activation in the left orbitofrontal cortex (t=4.7, FWE p=0.034; accuracy=54%, sensitivity=50%, specificity=57%).
Moreover, we did not detect longitudinal hippocampal subfield changes in treated acute depressed patients compared to pretreatment and control groups (interaction group×time F=2.99, p=0.05, no post-hoc tests significant). We found a significant effect of remission status (n=20, F=15.24, p<0.001), as well as a significant interaction of remission×time (F=8.14, p=0.004) in the right fimbria (MRI-1: t=2.8, p-Tukey =0.037, d=0.19), in the right presubiculum (MRI-1, t=2.55, p-uncorr =0.011, d=0.17) and in the right fissure (MRI-1: t=2.51, p-uncorr =0.012, d=0.17).
Conclusions: With 7T fMRI imaging, task-based and hippocampal subfield analysis we detected significant differences between remitter and non-remitter to first-line antidepressant treatments. The results show that structural and functional MRI at 7T is able to distinguish remitter from non-remitter in brain areas known to be affected by MDD. Yet, accuracies of distinguishing remitter from non-remitter of our results are just above chance. In conclusion, it might be advantageous to increase sample-sizes in longitudinal, pooled studies at widely available lower field-strengths to assess response prediction with MRI.

Learning Objectives:

1. Learn how hippocampal subfield volumes change according to antidepressant treatment.
2. Advantages and Disadvantages of 7T Imaging in longitudinal antidepressant trials.

Literature References:

1. Williams LM, Korgaonkar MS, Song YC, Paton R, Eagles S, Goldstein-Piekarski A, Grieve SM, Harris AW, Usherwood T, Etkin A. Amygdala Reactivity to Emotional Faces in the Prediction of General and Medication-Specific Responses to Antidepressant Treatment in the Randomized iSPOT-D Trial. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2015;40:2398-2408.
2. Gyurak A, Patenaude B, Korgaonkar MS, Grieve SM, Williams LM, Etkin A. Frontoparietal Activation During Response Inhibition Predicts Remission to Antidepressants in Patients With Major Depression. Biological psychiatry. 2016;79:274-281.
3. Hahn A, Kranz GS, Seidel EM, Sladky R, Kraus C, Kublbock M, Pfabigan DM, Hummer A, Grahl A, Ganger S, Windischberger C, Lamm C, Lanzenberger R. Comparing neural response to painful electrical stimulation with functional MRI at 3 and 7 T. NeuroImage. 2013;82:336-343.

COMBATTING ADOLESCENT DEPRESSION AND SUICIDE: PHARMACOTHERAPY WITH BRAIN DEVELOPMENT IN MIND

Jennifer Dwyer, Yale Child Study Center

Individual Abstract: Nearly one in four adolescents will experience major depressive disorder (MDD), and suicide is the 2nd leading cause of death in this age group. 40% of adolescents with MDD fail to respond to initial pharmacotherapy, and better treatments are urgently needed. While ketamine has rapid antidepressant and anti-suicidal effects in adults with treatment resistant-depression (TRD), there are no prospective placebo-controlled trials in adolescents. The adolescent brain is a unique pharmacologic substrate and the proposed sites of ketamine's action (e.g. prefrontal cortex and hippocampus) are actively maturing during this time. We conducted a midazolam-controlled crossover trial (n=17) to evaluate the effects of ketamine in adolescent TRD over four weeks. On day 1 and day 14 adolescents (13-17yo) received either ketamine (0.5mg/kg over 40 minutes) or midazolam (0.045mg/kg over 40

minutes). Subjects remained on their psychiatric mediations, with stable dosing, for the four weeks prior to the trial and the duration of the trial. A subset of subjects also underwent neuroimaging at baseline and 1 day following each treatment.
For the primary outcome, ketamine significantly decreased MADRS score 1 day following infusion compared to midazolam (p=0.03, n=17). Secondary outcomes included pediatric depression and anxiety scales, as well as treatment timecourse. Similarities and differences between these results and published adult studies will be discussed, and results will be framed in the context of what is known about the development of prefrontal glutamate systems during adolescence. These results provide important new data about ketamine's efficacy in the pediatric population and suggest the importance of evaluating the role of glutamate systems in the etiology of early-onset mood disorders.

Learning Objectives:

1. To understand the evidence base for the use of ketamine, a prototypic glutamatergic modulator, in pediatric mood disorders.
2. To appreciate the development of glutamatergic control of corticolimbic circuits during adolescence.

Literature References:

1. Dwyer JB, Beyer C, Wilkinson ST, Ostroff RB, Qayyum Z, Bloch MH. Ketamine as a Treatment for Adolescent Depression: A Case Report. J Am Acad Child Adolesc Psychiatry. 2017 Apr;56(4):352-354.
2. Caballero A, Granberg R, Tseng KY. Mechanisms contributing to prefrontal cortex maturation during adolescence. Neurosci Biobehav Rev. 2016 Nov;70:4-12.

KETAMINE TREATMENT MODULATES THE KYNURENINE AND ARGININE PATHWAYS IN DEPRESSED UNIPOLAR AND BIPOLAR PATIENTS

Bashkim Kadriu, National Institute of Mental Health

Individual Abstract: Preclinical and clinical studies suggest that the immune, monoaminergic, and glutamatergic systems are involved in the pathophysiology of depressive disorders. Risk of depression is known to be influenced by alterations of the innate and adaptive immune systems and their interaction with neurotransmitters and neurocircuitry. One potential confluence of these highly relevant systems occurs between the kynurenine (KYN) and arginine (ARG) pathways. Pathological activation of the KYN pathway via the rate-limiting enzyme indoleamine-2,3-dioxygenase (IDO) shifts two critical downstream byproducts—kynurenic acid (KynA) and quinolinic acid (QA)—that can trigger microglial activation, thereby altering glutamate release/reuptake. In addition, two components of the ARG pathway—arginine and citrulline—are critical substrates for protein synthesis as well as precursors to several important metabolites, including nitric oxide, that have been shown to be decreased in subjects with major depressive disorder (MDD). Increased peripheral pro-inflammatory cytokines, activation of the KYN pathway, and changes in the nitric oxide cycle likely alter the innate/adaptive immune system and decrease neurotrophic support, which may induce excitotoxicity. This symposium will explore the impact of the glutamatergic modulator ketamine on a series of peripheral biomarkers, including key components of the KYN and ARG pathways, in subjects with MDD and bipolar depression (BD) as well as healthy controls (HCs).
Data from two double-blind, randomized clinical trials assessing the efficacy of single-dose ketamine (0.5 mg/ kg IV) in treatment-resistant subjects with MDD or BD as well as HCs were included. Specific ELISA (BD group) and LC-MS-based metabolomics (MDD and HC subjects) were used to characterize components of the KYN and ARG pathways at baseline and at 230 minutes, Day 1, and Day 3 post-ketamine infusion.

In BD subjects, ketamine significantly decreased IDO levels and significantly increased KYN and KynA levels. Higher levels of anti-inflammatory—but not pro-inflammatory—markers were associated with lower baseline IDO levels and with higher baseline KYN and KYN/KynA levels in BD patients. A secondary analysis found that baseline KYN pathway levels predicted depressive symptoms post-ketamine at the trend level. In a separate metabolomic profiling study, lower circulating levels of citrulline and ARG were observed in MDD patients relative to HCs (19.2 ± 5.2 μM vs 23.8 ± 7.2 μM). Interestingly, in the MDD group, ARG levels increased significantly in ketamine responders; specifically, an increase of 16.6 ± 8.8 μM was observed in ketamine responders vs 7.1 ± 10.7 μM in ketamine non-responders at 230 minutes ($p = 0.005$).

Taken together, the results demonstrate that ketamine affects the KYN and ARG pathways, both of which are known to be altered in patients with MDD and BD. Interestingly, ketamine appears to affect the KYN pathway differently in MDD versus BD subjects. Ketamine also modulated the bioavailability of ARG in ketamine responders, indicating that ketamine may affect the nitric oxide cycle in subjects who respond to ketamine treatment.

Learning Objectives:

1. The kynurenine and arginine pathways are implicated in mood disorders.
2. The glutamatergic modulator ketamine may potentially modulate the neuroimmune pathway highly associated with depression phenotypes.

Literature References:

1. Miller, A. H. (2013). Conceptual confluence: the kynurenine pathway as a common target for ketamine and the convergence of the inflammation and glutamate hypotheses of depression. Neuropsychopharmacology, 38(9), 1607-1608. doi:10.1038/npp.2013.140
2. Moaddel, R., Shardell, M., Khadeer, M., Lovett, J., Kadriu, B., Ravichandran, S., . . . Zarate, C. A. (2018). Plasma metabolomic profiling of a ketamine and placebo crossover trial of major depressive disorder and healthy control subjects. Psychopharmacology (Berl). doi:10.1007/s00213-018-4992-7
3. Zarate, C. A., Jr., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., . . . Manji, H. K. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry, 63(8), 856-864. doi:10.1001/archpsyc.63.8.856

INDIVIDUALIZING ELECTROCONVULSIVE THERAPY FOR THE TREATMENT OF DEPRESSION

Zhi-De Deng, National Institute of Mental Health

Individual Abstract: Background: Electroconvulsive therapy (ECT) is the most effective treatment for severe treatment-resistant depression. However, ECT has significant cognitive side effects. A significant impediment to the optimization of ECT is the lack of rationally designed stimulation configurations that spatially target the brain structures hypothesized to mediate the antidepressant action of seizures, while avoiding regions that are thought to contribute to side effects. Competing theories of the therapeutic action of ECT hypothesize different optimal targets for seizure induction. Unfortunately, the lack of tools to selectively target these regions has impeded progress in testing these theories.

Methods: We introduce a novel form of ECT with several innovative features: 1) individualized low current amplitude titration; 2) state-of-the-art computational electric field modeling to individualized dosing; 3) multi-channel stimulation system coupled with multi-stimulation electrode array that allow flexible and optimal targeting of specific brain regions.

Results: In large scale computational modeling studies in ECT patients, we found that a fixed current of 800 mA produces marked variability in the induced intracranial electric field strength and spatial distribution. The current amplitude titration technique not only minimizes overexposure of the brain to suprathreshold tetanic electrical stimulation, but also compensates for inter-individual variability in head anatomy. We also show a high-density EEG recording of the induced seizure in a patient receiving conventional right unilateral ECT.
Conclusions: The next generation of seizure therapy is rationally designed, individualized, and neurotargeted. Multichannel stimulation coupled with high-density EEG can be used to inform further development of closed-loop stimulation systems for ECT.

Learning Objectives:

1. Describe the parameters that are important for dosing in electroconvulsive therapy.
2. Describe how computational modeling can help guide the individualization and targeting in ECT.

Literature References:

1. Deng ZD, Lisanby SH, Peterchev AV: Electric field strength and focality in electroconvulsive therapy and magnetic seizure therapy: a finite element simulation study. J Neural Eng 2011; 8:016007
2. Peterchev AV, Rosa MA, Deng ZD, Prudic J, Lisanby SH: ECT stimulus parameters: rethinking dosage. J ECT 2010; 26:159-174

CLINICAL TRIAL DESIGNS THAT MOVE PSYCHOPHARMACOLOGY TOWARDS PERSONALIZED MEDICINE

Lori Davis, Veterans Affairs Medical Center

Overall Abstract: This panel brings together inspired clinical scientists who will present their novel trial designs that have the potential to translate into personalized treatment approaches and inform "go-no-go" decisions in drug development for posttraumatic stress disorder (PTSD) and additionally when comorbid with alcohol use disorder. Dr. Hendrickson's presentation focuses on an aggregated n-of-1 design to investigate the noradrenergic biomarkers and predictive responses to treatment of PTSD with prazosin. Dr. Szabo's presentation focuses on neuroimaging and pupillometry as two surrogate biomarker endpoints in a proof-of-concept clinical trial of psychopharmacologic treatments for PTSD. Dr. Davis' presentation focuses on kappa opioid receptor antagonism to target a matrix primary outcome that combines World Health Organization risk level and PTSD symptoms in the treatment of comorbid PTSD and alcohol use disorder, a trial that also incorporated fear conditioning and psychophysiological paradigms to identify translational biomarkers.

Learning Objectives:

1. To better understand an aggregated n-of-1 design and noradrenergic biomarkers in predicting treatment responses to pharmacotherapy for PTSD.
2. To better understand neuroimaging and other biomarkers (pupillometry) in dose finding and response measurement in pharmacotherapy studies in the treatment of PTSD and MDD.
3. To better understand kappa opioid receptor antagonism in the treatment of PTSD and comorbid alcohol use disorder.

DESIGN AND EARLY RESULTS OF AN AGGREGATED N-OF-1 TRIAL OF PRAZOSIN FOR PTSD: AN EXAMPLE OF A NOVEL CLINICAL TRIAL DESIGN OPTIMIZED FOR BOTH BIOMARKER VALIDATION AND PARTICIPANT BENEFIT

Rebecca Hendrickson, VA Puget Sound Health Care System

Individual Abstract: Parallel-group randomized controlled trials are the gold standard for detecting differences in mean improvement across treatment conditions. They are poorly optimized, however, for quantifying the relationship of a biomarker measured at baseline to treatment response or identifying meaningful subgroups. Further, they often require that many participants spend the entire duration of the study on placebo, which can limit the enrollment of treatment-seeking or high-acuity patients.

In N-of-1 trials, an individual subject moves between several treatment conditions, such as active treatment and placebo, in order to determine the individual's specific response to each treatment. In aggregated N-of-1 trials, a cohort of individuals moves through this same type of trial design, and their outcomes are analyzed to answer questions about e.g. patterns of treatment response. Aggregated N-of-1 trials can be designed to optimize both statistical power and clinical or logistical constraints, such as allowing all participants to begin with an open-label stabilization phase to facilitate the enrollment of more acutely symptomatic participants.

Here, we will describe the development, validation and very early results of a novel, aggregated N-of-1 clinical trial design testing the ability of baseline biomarkers to predict PTSD treatment efficacy. Specifically, the trial is optimized to test the hypothesis that baseline measurements of noradrenergic biomarkers, including standing systolic blood pressure and pupillary dilation dynamics, will predict the degree of clinical improvement in participants' PTSD symptoms during treatment with the noradrenergic receptor antagonist prazosin. The trial, which begins with an 8-week phase in which all participant receive open-label treatment before moving to blinded discontinuation and then crossover phases, is also designed to maximize the clinical benefit and allow the referral of even very high-acuity, treatment-seeking patients.

We will particularly highlight in our presentation the highly generalizable aspects of this trial design, including the statistical process for optimizing the design for the observed parameters of treatment response to our intervention, and the flexibility of the analysis strategy. We will also discuss the early success of the trial in recruiting and retaining its target population, and in engaging both participants and referring providers in the overall goal of each participant ending their time in the trial with a clear understanding of their personal response to the treatment. We believe that this type of trial design represents a model that could be used in many areas of psychiatry to move psychopharmacology towards a personalized medicine model.

Learning Objectives:

1. Understand the limitations of a traditional, parallel group RCT to test hypotheses related biomarker validation and other personalized medicine goals, and how N-of-1 based trial designs avoid these pitfalls.
2. Understand the consequences of traditional, parallel group placebo-controlled trials for participant selection and experience, and how N-of-1 based trial designs can better serve the interests of trial participants while facilitating the recruitment of participants who better represent our true clinical populations.

Literature References:

1. Schork NJ: Personalized medicine: Time for one-person trials [Internet]. Nature 2015; 520:609–611Available from: http://www.nature.com/doifinder/10.1038/520609a
2. Raskind MA, Millard SP, Petrie EC, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, Hill J, Daniels C, Hendrickson R, Peskind ER: Higher Pretreatment Blood Pressure

Is Associated With Greater Posttraumatic Stress Disorder Symptom Reduction in Soldiers Treated With Prazosin. Biol. Psychiatry 2016; 80

CLINICAL TRIAL DESIGN AND NEUROBIOLOGICAL DRIVEN ENDPOINTS IN PTSD

Steven Szabo, Duke University Medical Centers

Individual Abstract: Purpose: Overview of clinical trial designs in PTSD using neurobiological endpoints as the primary outcome measure.
Content and Methodology: Neurobiological endpoints tethered to the pathophysiology of PTSD may strengthen clinical trial design. Assaying brain circuits linked to specified symptoms of PTSD may direct neurobiologically driven treatments proximal to disease pathology. Neuroimaging and pupillometry represent two surrogate biomarker endpoints of brain activity currently undergoing investigation in PTSD. Two clinical trials using these neurobiological endpoints are presented. These neurobiological markers are serving as the primary outcome measures in proof of concept clinical trials to psychopharmacologic Interventions in patients with PTSD. Symptom severity using the CAPS-5 represent the secondary endpoint measure.
Results: Target engagement and the ability to power studies on neurobiological endpoints can assist in dose finding and sample size reductions of the clinical trial. Neurobiological based endpoints can also inform on subject selection, patient heterogeneity, and translate into personalized treatment approaches in patients with PTSD.
Importance: Clinical trial designs which monitor symptom severity and have neurobiologically driven outcome measures based on the mechanism of action of the intervention are poised to inform on "Go/No Go" decisions at the proof of concept stage.

Learning Objectives:

1. Neurobiological endpoints as potential biomarkers of symptom severity in PTSD.
2. Clinical trial designs using neurobiological endpoints as primary outcome measures.

Literature References:

1. Szabo ST, Kinnon BJ, Brannan SK, et al.,: Lessons Learned and Potentials for Improvement in CNS Drug Development: ISCTM Section on Designing the Right Series of Experiments. Innov Clin Neurosci 2015; 12:11S-25S
2. Potter WZ: Optimizing early Go/No Go decisions in CNS drug development. Expert Rev Clin Pharmacol 2015; 8:155-157

NOVEL TRIAL DESIGN TO TEST KAPPA OPIOID RECEPTOR ANTAGONISM IN THE TREATMENT OF COMORBID PTSD AND ALCOHOL USE DISORDER

Lori Davis, Veterans Affairs Medical Center

Individual Abstract: Alcohol use disorders (AUD) and posttraumatic stress disorder (PTSD) are chronic costly illnesses that are associated with depression, premature death, risk of suicide, and disability. New treatment strategies are urgently needed. This presentation will discuss the rationale and methods for a study that will test a novel pharmaceutical treatment approach for Veterans and Service Members with comorbid AUD and PTSD. The objective of the study is to evaluate the efficacy and physiological effects of sublingual buprenorphine (SL-BUP; Subutex) combined with extended-release injectable naltrexone (XR-NTX; Vivitrol) in the treatment of comorbid AUD and PTSD. Sublingual buprenorphine, which acts as an antagonist at kappa and partial agonist of the mu receptors, combined with extended-release injectable naltrexone, which blocks the mu receptor, yields a pharmacologically net effect of kappa opioid receptor (KOR) antagonism. Concurrent use of naltrexone diminishes the potential of

buprenorphine misuse. The primary outcome is showing and categorical response that combines reduction in World Health Organization and the Clinician Administered PTSD Scale. In addition to the primary clinical outcomes for AUD and PTSD, pre- and post-treatment psychophysiological correlates of fear and alcohol craving that include 1) measure of the extinction of fear-potentiated startle and 2) psychophysiological reactivity to trauma stimuli and alcohol cues will be measured. Significance: AUD is highly prevalent in U.S. service members and among military Veterans and has a large detrimental impact on society. One important comorbid condition for individuals with AUD is PTSD. Finding a novel pharmacologic treatment approach to improve the clinical outcomes for Veterans and military Service-Members with comorbid PTSD and AUD is the focus of this project.

Learning Objectives:

1. To better understand the pharmacology of combination drugs that result in kappa opioid receptor antagonism and how this is potentially therapeutic for the treatment of comorbid PTSD and alcohol use disorder.
2. To better understand fear conditioning and psychophysiological arousal paradigms as potential biomarkers that predict or confirm treatment response.

Literature References:

1. Krystal JH, Davis LL, Neylan TC, A Raskind M, Schnurr PP, Stein MB, Vessicchio J, Shiner B, Gleason TD, Huang GD. It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group.. Biol Psychiatry. 2017 Oct 1;82(7):e51-e59. doi: 10.1016/j.biopsych.2017.03.007. Epub 2017 Mar 14.
2. Helal MA, Habib ES, Chittiboyina AG. Selective kappa opioid antagonists for treatment of addiction, are we there yet? Eur J Med Chem. 2017 Dec 1;141:632-647. doi: 10.1016/j.ejmech.2017.10.012. Epub 2017 Oct 10.

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

BIOMARKER DEVELOPMENT IN AUTISM: THE POTENTIAL IMPACT OF THE AUTISM BIOMARKERS CONSORTIUM FOR CLINICAL TRIALS (ABC-CT)*

Bernard Fischer, U.S. Food and Drug Administration

Overall Abstract: Developing treatments for autism spectrum disorders is challenging. For example, identifying a relevant population can be difficult in a syndrome that varies in phenotypic presentation and severity and likely has multiple underlying causes. Clinical trials are also resource-intensive when functional improvements in the disorder are unlikely to be observed in short-term studies. Biomarker development in autism might provide better ways of discriminating patient populations and quantifying treatment response. In this panel session, we will review the development of biomarkers for autism. We will describe the process by which biomarkers are recognized by the U.S. Food and Drug Administration (FDA)—including the effect of the 21st Century Cures Act. We will review the current state of biomarker research in autism and discuss the most promising findings from the Autism Biomarkers Consortium for Clinical Trials (ABC-CT). Finally, we will discuss the potential impact of autism biomarkers on treatment development.

Learning Objectives:

1. Identify how biomarkers are recognized in the United States and the status of biomarkers in autism.
2. Identify the most promising biomarkers from the Autism Biomarkers Consortium for Clinical Trials (ABC-CT) and how they might affect treatment development.

THE FDA APPROACH TO BIOMARKER QUALIFICATION FOR DRUG DEVELOPMENT

Martine Solages, Center for Drug Evaluation and Research, Food and Drug Administration

Individual Abstract: Expanded use of biomarkers can improve drug development by reducing inefficiency and enhancing precision. Biomarkers can potentially refine diagnosis, identify patients who may be at greater risk for adverse events or more likely to respond to an intervention, and monitor response to treatment. There are several pathways for a biomarker to gain recognition. However, biomarkers that serve as endpoints in clinical trials that guide regulatory decisions must meet certain validity and reliability criteria in their intended context of use. FDA supports the development of biomarkers that meet this standard. The 21st Century Cures Act outlines a three-stage process for biomarker qualification. A biomarker which is qualified through this pre-competitive program will be in the public domain and may be used in any drug development program under its qualified context of use. This discussion will provide an overview of the Biomarker Qualification Program and describe the process by which investigators may submit biomarkers for review.

Learning Objectives:

1. Participants will appreciate how expanded use of biomarkers can improve the drug development process.
2. Participants will learn about the pathway for qualifying biomarkers for use in drug development programs as specified in the 21st Century Cures Act.

Literature References:

1. 1.Califf, RM: Biomarker definitions and their applications. Exp Biol Med 2018; 243:213-221
2. Zhao, X, Modur V, Carayannopoulos, LN, Laterza, OF: Biomarkers in pharmaceutical research. Clin Chem 2015; 61(11):1343-1353

THE AUTISM BIOMARKERS CONSORTIUM FOR CLINICAL TRIALS: STUDY DESIGN AND PROGRESS THROUGH INTERIM ANALYSIS

James McPartland, Yale Child Study Center

Individual Abstract: Recent scientific advances offer promise for the development of targeted treatment methods to improve social-communication in autism spectrum disorder (ASD). The development of targeted treatments is hindered by a lack of reliable and sensitive objective measures to identify subgroups likely to respond to specific treatments, to rapidly assess response to treatment, and to evaluate whether a treatment has affected the intended target. The Autism Biomarkers Consortium for Clinical Trials is a multisite biomarker development study designed to advance these objectives.

The goals of the ABC-CT are to: (1) establish sensitive and reliable objective EEG and eye-tracking (ET) assays of social communication in ASD for predicting and quantifying response to treatment, reducing heterogeneity of samples via stratification, indicating early efficacy, and demonstrating target engagement; (2) create a publicly accessible repository spanning genetics, biomarkers, and clinical and behavioral information; and (3) establish an infrastructure optimized for the conduct of future clinical trials.

Prior to commencing full-scale data collection, a feasibility study assessed 51 subjects (25 ASD, 26 TD) to ensure: standardization and viability of data collection across sites; valid and reliable implementation of experimental measures; effectiveness of data processing, extraction, and quality control procedures; and reliability of data management, upload, and sharing systems. The main study commenced in October 2016 and was designed to include 200

rigorously characterized children with ASD (6-11 years; IQ 60-150) and 75 typically developing (TD) control subjects at three time points (Baseline, 6 weeks, 24 weeks). Detailed manuals of procedures (MOPs) and identical biomarker acquisition hardware and software are intended to minimize variance in ascertainment across sites, and clinical characterization is standardized with a clinical MOP and regular teleconferences to ensure reliability. A unique study governance brings together diverse expertise to facilitate progress from discovery to biomarker qualification. To provide opportunity for confirming biomarker results in independent samples, several EEG and ET paradigms are harmonized with those utilized in EU-AIMS.

Enrollment closed on November 1, 2018, with approximately 389 participants enrolled in the main study (pending final evaluation of screening criteria) and 284 having reached 24-week visits. Data collection will conclude in June 2019. Data acquisition procedures have been highly successful, with valid data acquisition rates above 96% across biomarker data modalities and minimal longitudinal attrition.

The ABC-CT, and other consortia like it, are advancing the goal of clinically practicable biomarkers by investigating well-evidenced biomarkers in large, well-characterized cohorts in the context of a longitudinal design. Progress in these studies is laying groundwork for more sensitive and reliable measurement in clinical trials, and the use of economical and scalable biomarker technologies holds promise for eventual deployment in a broader range of clinical and research contexts.

Learning Objectives:

1. Name two potential uses of biomarkers for autism spectrum disorder.
2. Describe the scientific objective of the Autism Biomarkers Consortium for Clinical Trials.

Literature References:

1. McPartland, J. (2017). Developing clinically practicable biomarkers for ASD. Journal of Autism and Developmental Disorders. PMID: 28695438; PMCID: PMC5711569.
2. McPartland, J. (2016). Considerations in biomarker development for neurodevelopmental disorders. Current Opinion in Neurology, 29(2), 118-122. PMID: 26844621; PMCID: PMC4798424.

THE AUTISM BIOMARKERS CONSORTIUM FOR CLINICAL TRIALS: EEG AND ET AS DISCRIMINANT BIOMARKERS, TEST-RETEST VALIDITY, AND CORRELATION WITH CLINICAL STATUS

Sara Webb, University of Washington

Individual Abstract: We report on EEG and eye-tracking (ET) data from the ABC-CT interim analysis. The objective of the ABC-CT is to validate (bio)markers that can be used to reduce heterogeneity of samples via stratification, to indicate early efficacy, and to demonstrate target engagement. The EEG protocol included 4 experiments: (1) Resting EEG; (2) Faces ERP (Faces Upright response); (3) Visual evoked potential (to checkerboards); and (4) Biological motion perception (to human point-light displays). The ET protocol included 5 experiments: (1) Activity Monitoring (actors in shared activity); (2) Social Interactive (children at play); (3) Biological Motion; (4) Pupillary Light Reflex; and (5) Static (social) Scenes. The primary variable for ET was a composite score created from Activity Monitoring, Social Interactive, and Static Scenes.

Interim results assess feasibility of administration; (bio)marker discriminant validity (group differences), test-retest reliability, and relation to clinical status. Data are reported on 161 children with ASD (81% male) compared to 64 children with TD (66% male). Age did not

differ by group (ASD M= 8.7 [1.8]; TD M= 8.7 [1.6], p= .89) or site (p= .30). The TD group had higher IQ (ps< .01), as well as fewer autism behaviors (ps< .01).
EEG validity was defined as completion of 50% of the Resting EEG with data. At T1, 96% of participants provided valid acquired data. We present on the 2 primary EEG biomarker variables: (1) Slope of the EEG power spectrum during Resting was valid in 91% of participants and reflected >20 seconds of attended artifact free EEG segments (89% ASD; 97% TD), with similar rates by sex, and across age bins. The slope was similar between groups (p= .16; AUC= .55 [95% CI .46-.63]). Test-retest was excellent (TD ICC= .83; ASD ICC= .83). The slope was correlated with age in the TD (r= .41) but not in the ASD group (r= .01). There were no correlations with sex or IQ. (2) The Face Upright N170 latency during ABC-CT Faces was valid for 79% of the sample, with higher rates in the TD (92%) than ASD group (74%). The N170 latency differed between groups (p< .01); the TD group demonstrating faster N170 latency than the ASD group (AUC= .66 [95% CI: .58-.74]). Test-retest was adequate (TD ICC= .66; ASD ICC= .66), and the latency was correlated with age (TD r= -.48; ASD r= -.37) with faster response in older individuals. There was no relationship with sex or IQ.
ET validity was defined as completion of 3 of 16 blocks with valid data. At T1, 100% of the ET data was identified as valid. The ET composite score was valid in 98% of participants, with similar rates by group, sex, site, and age. The ASD group (M= .21 [.07]) percent looking at social features was lower than the TD group (M= .29 [.07]; p< .01). Discrimination was excellent (AUC= .78 [95% CI: .72-.85]). Test-retest was also excellent (ASD ICC= .79; TD ICC= .83). The composite was correlated with age in the TD group (r= .43) but not ASD group (r=.14). The composite did not correlate with sex nor IQ.
The N170 biomarker and the ET composite obtained promising results in interim analysis. Ongoing analyses evaluate appropriateness of additional biomarker properties, such as stability over time and sensitivity to change in clinical status.

Learning Objectives:

1. Understand how acquisition validity is defined and differs between methods.
2. Understand preliminary differences in discrimination, test retest and correlation with clinical status for the primary outcome measures.

Literature References:

1. Loth E, Spooren W, Ham LM, Isaac MB, Auriche-Benichou C, Banaschewski T, Baron-Cohen S, Broich K, Boelte S, Bourgeron T, Charman T. Identification and validation of biomarkers for autism spectrum disorders. Nature Reviews Drug Discovery. 2016 Jan;15(1):70.
2. Klin A. Biomarkers in autism spectrum disorder: challenges, advances, and the need for biomarkers of relevance to public health. Focus. 2018 Apr 27;16(2):135-42.

THE ROLE OF BIOMARKERS IN THE DEVELOPMENT OF NOVEL THERAPEUTICS FOR AUTISM SPECTRUM DISORDER: FROM EARLY TO LATE DEVELOPMENT, AND FROM STRATIFICATION TO CHANGE DETECTION

Gahan Pandina, Janssen Research & Development, LLC

Individual Abstract: Autism Spectrum Disorder (ASD) is a complex, heterogeneous neurodevelopmental disorder with no approved medications for treatment of core symptoms. A biomarker, "… a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions - objective measures" (FDA, www.fda.gov), has the potential to de-risk ASD drug development by improving patient selection and enhancing sensitivity to drug response. Potential biomarkers range from blood-based to imaging, to more experimental markers such as biosensors. These include electroencephalography (EEG) and eye-tracking.

Sensors represent a non-invasive, standardized, easy-to-employ method that may help objectively measure complex ASD symptoms. Current ASD clinical trials use caregiver or clinician rating scales to assess outcome. While scales provide information about the subject's clinical status, they are subjective, and have not been extensively used in drug trials, particularly over short time intervals.

Biomarkers are common in therapeutic areas where the disease target or underlying pathology is biologically well-defined. In heterogeneous disorders such as ASD, biology is multifactorial or yet to be elucidated. Thus, we face a number of challenges at different stages of drug development.

Early proof-of-concept (PoC) studies test short-term efficacy, safety, and tolerability in small samples. In PoC studies, a set of known biomarkers could help to stratify or enrich a population and create a population subset more likely to be drug-responsive or linked to drug mechanism of action. As trials are short and treatment effect is unknown, an objective measure of early change at PoC may help increase detection of drug effect. Biomarkers could also distinguish a negative (i.e. a true no drug effect) from a failed study (e.g. procedures were flawed or poorly executed).

PoC studies provide evidence to progress to confirmatory drug studies (Phase 2B/3). Phase 2b/3 studies confirm short-term efficacy, safety and dose, and establish longer-term safety, tolerability and effectiveness in a broad population. A Phase 2B/3 biomarker could be a threshold for trial inclusion, or a gauge of severity. It could also measure stability of treatment effect over time (i.e. biologic need) or help determine a therapeutic dose.

Most studies of ASD biomarkers are small. Multicenter consortia in Europe and North America have begun to standardize research approaches, using sensors combined with computer-based stimuli designed to elicit responses to ASD-specific neurobiology. Findings from these studies are more robust. Social communication deficits detected via assessment of gaze duration and eye-gaze patterns during viewing of dynamic social scenes show that individuals with ASD do not have a natural face-gaze preference. ASD individuals may also have difficulty shifting eye-gaze from non-social scenes in static arrays. EEG studies show inefficient processing of social information in ASD, and over-recruitment of brain regions or altered patterns of connectivity during viewing of social scenes. Other experiments find both eye-tracking and EEG task-based performance deficits or inefficiencies. These correlate only modestly with clinical symptoms, suggesting differential utility of these measures. Ongoing investigations hope to establish utility of potential biomarkers in clinical trials.

Learning Objectives:

1. To understand the potential impact of the development of novel biomarkers on drug development approaches in ASD.
2. To identify recent examples of recent results from computer-based tasks and eye-tracking and electroencephalography studies in ASD.

Literature References:

1. Ness SL, Manyakov NV, Bangerter A, Lewin D, Jagannatha S, Boice M, Skalkin A, Dawson G, Janvier YM, Goodwin MS, Hendren R, Leventhal B, Shic F, Cioccia W and Pandina G (2017). JAKE® Multimodal Data Capture System: Insights from an Observational Study of Autism Spectrum Disorder. Front. Neurosci. 11:517. doi: 10.3389/fnins.2017.00517.
2. Manyakov N, Bangerter A, Chatterjee M, Mason L, Ness S, Lewin D, Skalkin A, Boice M, Goodwin M, Dawson D, Hendren R, Leventhal B, Shic F, Pandina G (2018). Visual Exploration in Autism Spectrum Disorder: Exploring Age Differences and Dynamic Features Using Recurrence Quantification Analysis. Autism Research, 11, 1554–1566.

PHARMACOGENOMIC TESTING IN PSYCHIATRIC PRACTICE: DOES IT DELIVER WHAT IT PROMISES?*

Angelos Halaris, Loyola University Chicago Stritch School of Medicine

Overall Abstract: Pharmacogenomics or the science of specific genes controlling the expression of proteins that are responsible for metabolizing pharmacotherapeutic agents, and also a host of biochemical processes in the body such as neurotransmission, are of major relevance to psychiatric practice. Pharmacogenomics has been gaining acceptance, albeit slowly, in medical practice in general and particularly in psychiatric practice, as will be described in detail in this symposium. The presenters have expertise in this field and will present the scientific underpinnings of pharmacogenomics in the use of psychotropic agents and will discuss pharmacodynamic issues that may impede treatment response and lead to resistance.

The overarching goal of striving to practice personalized medicine is significantly aided by pharmacogenomic testing and marketed products offer pharmacogenomics panels citing evidence that the results improve outcomes for patients with a psychiatric diagnosis, notably a depressive disorder. Especially in affective disorders the rates of treatment response and remission are particularly low, with no more than one third of MDD patients achieving remission and often requiring several "trials and errors" before achieving an acceptable response. A major contributing factor to treatment non-response is incompatibility between the chosen pharmacologic agent and the genetic makeup of the patient, which controls the expression of specific enzymes known as the cytochrome P450 system expressed in the liver. This system is largely responsible for metabolizing externally delivered compounds and thereby rendering them inert and able to be excreted from the organism thereby detoxifying the body. Depending on the marketed panel, additional and relevant genes are tested, referred to as pharmacodynamic genes, such as the serotonin transporter, the serotonin receptor 2A and the HLA alleles. The latter are responsible for mediating dermatologic reactions that could lead to serious outcomes. Over decades the choice of, for example, an antidepressant agent, was based on the patient's presenting symptoms and history of illness including prior trials of failed or successful treatment regimens, the STARD guidelines, and the practitioner's best, educated guess. This "hit or miss" approach has been the modus operandi for a long time until the concept of pharmacogenomic guidance in the decision-making tree by the practitioner became reality. So, given the obvious advantage to pharmacogenomic testing, why hasn't it yet found wide acceptance? One reasonable answer is that it takes time for any innovation to receive wide acceptance. However, in this specific area of endeavor, prior study shortcomings, notably small numbers of genes and variants available for validated testing, small sample sizes and short durations of trials have contributed to skepticism on the part of practitioners. To advance research, combinatorial pharmacogenomic (PGx) algorithm advances now integrate multiple pharmacokinetic (PK) and pharmacodynamic (PD) genes enabling more accurate predictions of response to a specific agent. Details of such testing will be elaborated on by the presenters. Additionally, published studies will be discussed, highlighting the findings of prospective blinded studies that have confirmed the value of pharmacogenomic testing both in terms of significantly improved treatment outcomes as well as associated health care cost savings.

Learning Objectives:

1. Participants will be able to define pharmacogenomics and appreciate the significant contribution of this scientific breakthrough in implementing personalized medicine in psychiatric practice.
2. Participants will be able to discuss the published data in the literature and appreciate the value of retrospective versus prospective studies illustrating the importance of conducting such testing in specific psychiatric disorders.

PSYCHOPHARMACOGENOMICS IN PRACTICE: AN OVERVIEW

Katherine Johnson, Loyola University Chicago Stritch School of Medicine

Individual Abstract: Pharmacogenomic testing is an innovative and highly promising tool for managing pharmacotherapy and helping to personalize treatment in a more efficient manner. It is currently employed in multiple disciplines such as Oncology, Hematology, Pain Management, and Psychiatry. This test has the potential to be a particularly useful tool when choosing psychiatric medications. We often struggle with the "trial and error" of choosing the most appropriate pharmacotherapeutic agent for our patients, as our medication arsenal is mostly pluripotent. We know that genetics and epigenetics play a role in these illnesses as well as in medication responsiveness, but we also know that trauma, environment, and even individual experiences of a stimulus can cause differences across individuals at a neurochemical and neuroanatomical level, rendering medication response difficult to predict. What works well in one patient may work very differently in another, and medications within the same class can have very different efficacy and side effect profiles within the same patient. Additionally, psychiatric medications have the highest number of pharmacogenomic biomarkers identified by the FDA. Thus, one tool for helping to streamline and personalize this process is to employ pharmacogenomic testing. Combinatorial pharmacogenomics takes this a step farther, integrating both pharmacokinetic markers in proportion to their relative clearance of a drug (as most use more than one pathway) and pharmacodynamic genes. In this lecture, we will provide a general overview of pharmacogenetics and the role of small mutations in the larger picture. We will discuss the commercially available testing, with a focus on the combinatorial phamacogenomic testing utilized by our institution. We will review the available data validating this tool and briefly discuss the process for generating the individual data. We will discuss the role of this test in clinical practice, with particular focus on the practicalities of use in an outpatient setting. We will also extensively discuss the limitations of this testing and the context in which it is best utilized, and how to apply this testing in a thoughtful and holistic manner informed by patient interaction. Additionally, as the majority of patients with mental health complaints present to primary care physicians initially, and as the US moves towards a more integrated and collaborative model of care between psychiatric specialists and primary care providers, we will discuss the role of this testing in a primary care setting and in a collaborative model.

Learning Objectives:

1. Participants should be able to elaborate the practical utility of phamacogenomic testing in psychiatric practice.
2. Participants should be able to elaborate the limitations of phamacogenomic testing in psychiatric practice.

Literature References:

1. Greden et al. Combinatorial pharmacogenomics significantly improves response and remission for major depressive disorder: a double-blind, randomized control trial. Poster session presented at: American Psychiatric Association Annual Meeting; 2018 May 5-9; New York, NY.
2. Winner, et al. A Prospective, Randomized, Double-Blind Study Assessing the Clinical Impact of Integrated Pharmacogenomic Testing for Major Depressive Disorder. Discovery Medicine, 2013, 16:89, pp 219-227

PHARMACOGENOMIC TESTING IN PSYCHIATRIC PRACTICE: DOES IT DELIVER WHAT IT PROMISES?

John Greden, University of Michigan

Individual Abstract: Background and Methods: Pharmacogenomic testing has not yet been routinely adopted by clinicians as an approach for improving outcomes in patients with Major Depressive Disorder (MDD). Many remain skeptical or puzzled about such tests. There are several reasons. Shortcomings in early studies and publications included small numbers of genes and variants, small sample sizes and short durations for follow-up. While much work remains to be done, test shortcomings are being addressed. Another expressed concern was that pharmacogenomic tests have not yet been able to convey which medications are statistically shown to be most effective. Combinatorial pharmacogenomic (PGx) algorithm advances are progressively integrating and evaluating multiple pharmacokinetic (PK) and pharmacodynamic (PD) genes. Interpreting test results can be moderately complex.

To address prevailing concerns, we employed a combinatorial pharmacogenomics test (GeneSight) and evaluated 1,167 patients with MDD and prior inadequate response to antidepressants, in a blinded, 24-week trial. At week 8, in this previously treatment-resistant population, symptom improvement for guided-care was not significantly different than TAU (27.2% versus 24.4%, p=0.107); however, improvements in response (26.0% versus 19.9%, p=0.013) and remission (15.3% versus 10.1%, p=0.007) were statistically significant. Patients taking incongruent medications—a term that is important to understand--prior to baseline who switched to congruent medications by week 8 experienced greater symptom improvement (33.5% versus 21.1%, p=0.002); greater response (28.5% versus 16.7%, p=0.036); and greater remission (21.5% versus 8.5%, p=0.007) compared to those remaining incongruent. Combinatorial pharmacogenomic testing thus significantly improved response and remission rates for difficult-to-treat depression compared to standard of care. (ClinicalTrials.gov NCT02109939)

Conclusions: Clinicians must continue to pursue precision health biomarkers with patients with MDD, perhaps most important for those who have been treatment resistant, but valuable for all. Rigorous methodological designs will be required. Additionally, a major conceptual barrier that will need to be better understood, is that combinatorial pharmacogenomic test results do not yet determine beforehand which antidepressant may be most effective for a patient. Emerging data now show, however, that such tests aid in conveying which medications may be "incongruent" choices and incorrect for a given patient. In this study, that process aided attainment and perpetuity of response and remission.

Learning Objectives:

1. Describe clinical improvements provided by pharmacogenomic testing for clinical response and remission.
2. Describe that such tests do not yet convey which medications are MOST effective.

Literature References:

1. Rosenblat, J.D., Lee, Y., McIntyre, R.S., 2017. Does Pharmacogenomic Testing Improve Clinical Outcomes for Major Depressive Disorder? A Systematic Review of Clinical Trials and Cost-Effectiveness Studies. J Clin Psychiatry 78(6), 720-729.
2. Swen JJ, Nijenhuis M, van Rhenen M, de Boer-Veger NJ, Buunk AM, Houwink EJF, Mulder H, Rongen GA, van Schaik RHN, van der Weide J, Wilffert B, Deneer VHM, Guchelaar HJ; Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Pharmacists Association (KNMP). Pharmacogenetic Information in Clinical Guidelines: The European Perspective.
3. Clin Pharmacol Ther. 2018 May;103(5):795-801. doi: 10.1002/cpt.1049. Epub 2018 Mar 30.

THE USE OF PHARMACOGENOMICS IN MEDICAL PRACTICE: WHAT ABOUT PSYCHIATRY?

Simon Kung, Mayo Clinic

Individual Abstract: Pharmacogenomics is increasingly used in the field of medicine. While there is controversy about its use for selecting antidepressants, how is it used for non-psychiatric applications? In this session, we review the rationale behind pharmacogenomics, its use in medical applications, and possible barriers for its use in psychiatry.

First, we present the genetic basis of pharmacogenomics consisting of pharmacokinetics and pharmacodynamics. For pharmacokinetics, the cytochrome P-450 enzyme metabolism system, specifically 2D6, 2C19, 3A4/5, and 1A2, will be explained. Geographic and racial differences in genetic polymorphisms will be highlighted. Alterations in genotype lead to slower or faster phenotype (enzyme activity).

Second, the use of clopidogrel and warfarin (anticoagulation medications) and simvastatin (for cholesterol lowering) will be discussed. The evidence for genotype-guided dose adjustments will be reviewed, drawing from the CPIC (Clinical Pharmacogenetics Implementation Consortium) guidelines. A randomized trial of pharmacogenomics-guided versus traditional warfarin dosing, favoring the use of pharmacogenomics, will also be reviewed.

Third, we review the pharmacogenomics of analgesic medications, which came more into public awareness after pediatric fatalities from prescriptions of codeine in susceptible patients. Polymorphisms in 2D6 and 3A5 can affect levels of opioid medications, which is relevant with the national opioid epidemic. There is still conflicting data about the OPRM1 mu-opioid pain receptor and its role in analgesia and opioid requirement.

Finally, we discuss the possible barriers of pharmacogenomics in psychiatry, despite the growing evidence of its benefits. Further education about pharmacogenomics for clinicians and patients, including its limitations, are needed. Further industry-neutral research of patient outcomes is also needed.

In conclusion, pharmacogenomics provides useful information about medication selection and adjustments, which improves patient outcomes, in many medical settings. The use of pharmacogenomics in psychiatry settings will be an important field moving forward.

Learning Objectives:

1. Participants will be able to discuss the medical applications of pharmacogenetics such as for warfarin or clopidogrel.
2. Participants will be able to describe some of the barriers for pharmacogenetics use in psychiatry.

Literature References:

1. Pirmohamed M., Burnside G., Eriksson N., et al. A Randomized Trial of Genotype-Guided Dosing of Warfarin. N Engl J Med 2013; 369:2294-2303
2. Zubenko GS, Sommer BR, Cohen BM. On the Marketing and Use of Pharmacogenetic Tests for Psychiatric Treatment. JAMA Psychiatry 2018;75(8):769-770, doi: 10.1001/jamapsychiatry.2018.0834

DIGITAL TECHNOLOGY ADVANCEMENTS AND POTENTIAL FOR ASSESSING BEHAVIOR IN CLINICAL TRIALS*

Jean-Pierre Lindenmayer, New York University

Overall Abstract: Mobile digital technology, such as mobile, sensory and robotic devices represent a potential new resource for research and treatment of mental illness. The convergence of increasing patient ownership of digital devices and an emerging literature on

their effect on assessment, diagnostic as well as therapeutic utility has been remarkable in the last few years. In addition, digital technology has become critical in driving more efficient and accurate data collection through all stages of research and development. The ease of use of digital technology in clinical trials has provided new data and treatments, such as patient-reported outcomes through mobile and sensor technology, robot-assisted interventions and virtual reality programs to deliver rehabilitation interventions.

However, the implementation of these technologies in psychiatric treatments and as efficacy outcomes in clinical trials necessitates greater scientific evidence of their reliability and validity. Several questions regarding design, patient acceptance of this technology, the integration of the technology in their everyday life and their biological/physiological mechanisms remain.

In this panel, we provide examples of digital technology research and of how these technologies, guided by clinical experts, are being implemented in clinical trials. We will highlight the technological advances to demonstrate how collaborative clinical research efforts are helping to build the scientific evidence base for the use of novel technology in state-of-the-art care for individuals with mental illness. The following four topics will be discussed:

Paul Dagum (Mindstrong Health) will present "Digital Phenotyping: Integrating mobile and sensor technology through passively collected smartphone behavioral data". The aim of this digital system is to monitor patients through a smartphone app in order to identify possible warning signs of relapse and readmission. The data obtained by passive data capture is entered in an AI program to detect activity patterns specific to the patient.

Anzalee Khan, PhD (Nathan Kline Institute for Psychiatric Research) will address a digital system, which integrates electronic patient-reported outcome (PRO) measures into routine practice for real-time symptom monitoring, as recognized by the FDA in its Guidance for Industry on Patient-Reported Outcome Measures.

Nanea Reeves, B.A. (TRIPP) will explore virtual reality as therapy. As virtual reality (VR) software becomes more sophisticated, users are able to interact with the environment through multiple senses. VR can distract and redirect attention away from unpleasant stimuli, such as traumatic thoughts, or fears, allowing a patient to spend time with calming activities. It can also provide effective graduated exposure therapy for specific phobias or help recovering addicts with triggering stimuli. Additionally, VR can motivate patients to engage in rehabilitation therapy through technology similar to that used to create games, making the treatment fun or competitive.

Corey Fowler, PhD (Otsuka Pharmaceuticals) will present on digital applications for conduct of virtual clinical trials in SMI patients. Virtual trials present new patient centric opportunities to reduce placebo response and enroll more diverse patient groups while introducing new challenges toward measurement of traditional psychometric assessments in a remote environment. Technology and new innovations to combat these challenges will be presented.

Discussant: Jean Pierre Lindenmayer, MD (New York University)

Learning Objectives:

1. Participants will have a better understanding of the diagnostic as well as therapeutic utility of digital technology for accurate data collection through all stages of research and for treatment indications.
2. Participants will receive better insight in the reliability and in clinical correlations of data gathered by digital technology.

DIGITAL BIOMARKERS OF DEPRESSION RELAPSE AND REMISSION

Paul Dagum, Mindstrong Health

Individual Abstract: Measurement-based care in behavioral health hinges on clinically-actionable biomarkers that can detect and predict illness relapse. We present clinically useful digital biomarkers based on touchscreen interactions captured passively from smartphone use. In a private outpatient psychiatric clinic, using a commercial app, smartphone touchscreen patterns were collected longitudinally on adult patients being treated for depression. Daily smartphone use data on patients were correlated with longitudinal clinical mood assessments through serial measures of clinical change. Machine learning algorithms were used to create digital biomarkers correlated with clinical ratings: Hamilton Depression (HamD), Hamilton Anxiety (HamA), Smith Hamilton Pleasure Scale (SHAPS) and Clinical Global Impression of Severity (CGI-S). These are the first results using digital phenotyping to develop a clinically actionable biomarker for the treatment of depression. This approach could serve as an early signal of patients at risk of relapse.

Learning Objectives:

1. Digital phenotyping.
2. Clinical (digital) biomarkers of depression.

Literature References:

1. Dagum, P (2018). Digital biomarkers of cognitive function. NPJ Digital Medicine, 1(10).
2. Insel, T. R. (2017). Digital phenotyping: technology for a new science of behavior. JAMA, 318(13), 1215-1216.

INTEGRATING ELECTRONIC PATIENT-REPORTED OUTCOME (PRO) MEASURES INTO PRACTICE FOR REAL-TIME SYMPTOM MONITORING

Anzalee Khan, VeraSci and Nathan S. Kline Institute for Psychiatric Research

Individual Abstract: Interest in the self-perception of individuals with schizophrenia is increasing because of the gap between the physician and patient's perceptions of symptom, and the technological resources to gather information more frequently and ecologically more valid from community dwelling patients. Clinical trials for schizophrenia are increasingly using electronic methods to collect patient-reported outcomes (ePRO). Hence, several ePROs have been developed to better understand patients' experience with their own illness. ePRO instruments are important when measuring concepts best known by the patient or best measured from the patient's perspective. Additionally, ePRO offers confidentiality since information is collected directly from patients without the involvement of another human being, which may interfere with patient response on delicate topics. In most clinical settings or clinical trials, an assessment is completed at an agreed upon visit (usually 1 week to 1 month following the last visit). Full psychosocial and medical assessments of all patients in a high-volume clinic may not be feasible due to limited resources and demand for services. As a result, we are forced to rely on physicians to identify symptoms and functional limitations. This approach could fail to identify patients in need of support. In clinical trials during the time between visits, the patient may have changes in symptomatology or quality of life that is not captured. Proper and early recognition of psychosocial need may result in prompt intervention, improvement in outcome of co-occurring physical and mental illness, faster recovery, and reduce the potential for relapse.

Advances in technology have facilitated the collection of Electronic Patient Reported Outcomes (ePROs) to improve clinical care and support clinical trial efforts. ePRO systems can utilize web-based applications and/or tablet devices to collect and send data on symptoms, substance use, sleep, pain, and quality of life domains in real time. Routine assessment of patient-reported outcomes (PROs), including symptoms, function, and quality of life, have been reported to lead to improvement in symptom management (Basch et al., 2009),

identification of psychosocial problems (Cunningham et al., 2018) and patient-provider communication.
This session will cover ePRO data collection technologies, compliance with use of ePRO in a psychiatric population, results from an ongoing clinical trial utilizing an ePRO (e.g., for assessment of insight into illness, for identification of relapse, and level of engagement with treatment), and integrating ePRO outcomes with other endpoints obtained from passive digital phenotyping, and standard clinical assessments.

Learning Objectives:

1. The participant will be able to identify feasibility of using ePRO in clinical settings and clinical trials for patients with schizophrenia who have had multiple hospitalizations.
2. Participants will be provided with information on patient attitudes towards electronic PRO assessment and learn how ePROs compare to standard clinical assessments measuring the same construct (primarily in relation to lack of insight into illness, and engagement).

Literature References:

1. Wintner LM, Giesinger JM, Zabernigg A, et al. Evaluation of electronic patient-reported outcome assessment with cancer patients in the hospital and at home. BMC Med Inform Decis Mak. 2015;15:110.
2. Reininghaus, U., & Priebe, S. (2012). Measuring patient-reported outcomes in psychosis: Conceptual and methodological review. British Journal of Psychiatry, 201(4), 262-267. doi:10.1192/bjp.bp.111.107615

PATIENT CENTRICITY IN VIRTUAL CLINICAL TRIALS

Corey Fowler, Otsuka Pharmaceuticals

Individual Abstract: Virtual Clinical Trials present new patient centric opportunities to reduce placebo response and enroll more diverse patient groups while introducing new challenges toward measurement of traditional psychometric assessments in a remote environment. Employing telemedicine, a study was designed to test the ability of stable patients diagnosed with Major Depressive Disorder to engage via two distinct virtual methods: (1) remote visits from mobile healthcare professionals who collected vitals and labs coupled with telemedicine for psychometric assessment evaluation, and (2) study-in-a box Bluetooth enabled devices for self-administered collection of vitals and remote lab collection coupled with telemedicine to guide patient collection of remote measures and to perform psychometric assessments. Results presented herein identify challenges faced in real-world settings inclusive of scheduling and logistics, patient compliance, and psychometric assessment validity. Conclusions gained from this trial support the validity of virtual clinical trials in a psychiatric patient population while also suggesting that further development is needed to combat technological challenges of telemedicine safety assessments.

Learning Objectives:

1. To identify challenges and opportunities in development of virtual clinical trials in Serious Mental Ill patients.
2. To understand methodologies employed that challenge currently accepted standards yet maintain patient safety.

Literature References:

1. Psychiatr Services. 2007;58(6):836–43.
2. J Gen Intern Med. 2007;22(8):1086–93.

MOVING FROM VIRTUAL REALITY EXPOSURE TO EMBODIED TREATMENT
Nanea Reeves, TRIPP

Individual Abstract: Recently expanded brain plasticity theories and findings about the ability of the cellular synapses to reconstruct the nervous system due to interaction with enriched environments have impelled new research. As a consequence, interventions utilizing virtual reality (VR), a non-invasive non-pharmacological treatment, have gained interest. The therapeutic goal of VR is oriented to stimulate, restore or engage the brain processes in order to maximize the patient's ecological autonomy and quality of life. The main properties offered by VR technology is the high engagement and real-time interaction. As a patient is navigating through a VR system, a sense of presence in the VR environment is a major mechanism that enables behaviors to be felt. Additionally, VR systems can deploy gamification, or use of game design elements in non-game contexts, incorporating elements like collecting points/coins, and external rewards to encourage learning. Understanding individuals with psychotic and related disorders requires consideration of patients' interactions in the social world. In patients with psychiatric disorders, VR, can allow patients to work through their own fears in a no-risk environment. Additionally, negative symptoms, for example, asociality, anhedonia, blunted affect, active social avoidance, all reflect difficulties in social interactions, leading to lack of engagement with others and lack of motivation. VRs ability to create an interactive world for otherwise disengaged patients, suitably applied, holds great promise in furthering the understanding and treatment of psychosis.
The presentation will focus on VR technology applied in clinical settings as an adjunctive treatment for individuals suffering from mental health disorders. Previously, technological and cost barriers have limited the use of VR to the private sector. The introduction of mobile VR headsets, presents an opportunity to use telemedicine and exposure therapy among others for mental health treatment

Learning Objectives:

1. To understand the application of Virtual Reality in clinical practice and clinical trials.
2. To attain information on how to successfully implement Virtual Reality programs in practice and clinical trials.

Literature References:

1. Gregg L, Tarrier N. Virtual reality in mental health. Soc Psychiatry Psychiatr Epidemiol. 2007;42:343–354.
2. Bermudez I Badia S, Velez Quintero L, Cameirao MS, Chirico A, Triberti S, Cipresso P, Gaggioli A. Towards Emotionally-Adaptive Virtual Reality for Mental Health Applications. IEEE J Biomed Health Inform. 2018 Oct 31.

ISCTM/ASCP WORKSHOP – DEVELOPING AN ADVANCED CNS CLINICAL TRIAL COURSE
Carla Canuso, Janssen Research & Development

Overall Abstract: This is an especially exciting, yet still challenging, time for the field of CNS drug development. While we have witnessed a growth in the number of novel CNS compounds in development, as well as the emergence of new technologies for assessment and disease management and more evidenced based psychosocial treatments, there is the need for well-trained and methodologically savvy clinical trialists to ensure the scientific and regulatory success of new and future CNS treatments. The American Society of Clinical Psychopharmacology (ASCP) and International Society of CNS Clinical Trials and Methodology (ISCTM), with their complementary missions and member expertise, see the

need for an educational offering that goes beyond a basic course in clinical trial design, methods and statistical analysis. As such, the two Societies have joined forces to develop a more advanced, 1 or 2-day course on clinical trials to support the development of CNS therapeutics, which will take place in the first half of 2020. The course target audience is envisioned to be multidisciplinary, mid-career individuals from Industry, Academia and Regulatory bodies who are designing, implementing and evaluating clinical trials.

A Joint Steering Committee, comprised of experts with a wide range of experience in CNS drug development and clinical trial design, has been convened to select curriculum topics and identify a faculty to develop content and teach the course. As an initial step in assessing needs and interests, the Joint Steering Committee will field a survey of the ASCP and ISCTM members. The Joint Steering Committee will present the course objectives, the survey results and proposed curriculum topics in a Workshop at the 2019 Annual ASCP meeting. The Workshop will allow interested stakeholders to provide additional suggestions and feedback on the curriculum.

Learning Objectives:

1. Participants will understand the greatest challenges in the development CNS therapeutics, and the results of a survey identifying current learning needs of those designing, implementing and evaluating CNS clinical trials.
2. Participants will learn about a proposed curriculum for a 1- or 2-day advance course on CNS clinical trials developed by an ISCTM/ASCP Joint Steering Committee.

Pharmaceutical Pipelines
1:50 p.m. - 4:00 p.m.

THE SELECTIVE OREXIN-1 RECEPTOR INHIBITOR JNJ-61393215 DECREASES SUBJECTIVE ANXIETY EVOKED BY 35% CARBON DIOXIDE INHALATION IN HEALTHY SUBJECTS

Giacomo Salvadore*[1], *Sander Brooks*[2], *Cathy Bleys*[1], *Kanaka Tatikola*[1], *Bart Remmerie*[1], *Gabriel Jacobs*[2], *John Moyer*[1], *Abigail Nash*[3], *Luc Van Nueten*[1], *Wayne Drevets*[1]
[1]*Janssen Research & Development,* [2]*CHDR,* [3]*Janssen Scientific Affairs*

Abstract: Background: JNJ-61393215 is a novel, selective, high affinity/potent orexin-1 receptor (OX1R) antagonist and is a potential first in class therapy for the treatment of panic, anxiety, PTSD, mood disorders and substance abuse. OX1R inhibitors show anxiolytic effects in several preclinical behavioral paradigms, including fear conditioning, fear potentiated startle, lactate infusion, hypercapnia, and yohimbine challenge. Activation of the OX1R is a critical component of CO2-mediated anxiety. JNJ-61393215 blocked CO2-induced anxiety behavior in the social interaction test at 10 and 30 mg/kg (p.o.) in a rat model of CO2-induced panic.

Inhalation of CO2 induces anxiety symptoms and panic attacks in subjects with anxiety disorders as well as healthy subjects, and benzodiazepines attenuate those symptoms. In the current study, the anxiolytic effects of JNJ-61393215 were investigated in humans using an experimental medicine model of CO2 inhalation.

Methods: To investigate the potential anxiolytic effects of JNJ-61393215 in humans, 39 healthy male subjects sensitive to the anxiogenic effects of 35% CO2 inhalation at screening were randomized to receive JNJ-61393215 25mg QD (extrapolated peak receptor occupancy: 93%), JNJ-61393215 90mg QD (extrapolated peak receptor occupancy: 98.5%), alprazolam 1mg bid or placebo for 7 days. The study used an incomplete cross-over design and each subject was

randomized to receive either placebo or one of the three active treatments. Subjects underwent a 35% CO2 inhalation challenge after 6 days of dosing with the study drug in each cross-over period and anxiety symptoms induced by the CO2 challenge were measured using the Panic Symptom List (PSL-IV). The CO2 challenge was performed 2.5 hours after the administration of the study drug (Tmax median: 1.5h; range: 1-3h); alprazolam was used as active comparator to establish assay sensitivity, to compare the magnitude of changes in the PSL-IV induced by JNJ 61393215 or alprazolam versus placebo.
Results: JNJ-61393215 90mg induced a statistically significant reduction of anxiety symptoms induced by inhalation of 35% CO2 in healthy volunteers according to the primary outcome measure PSL-IV (difference of LS Means vs. placebo: -2.3; $p<0.02$); a significant anxiolytic effect was also demonstrated for a therapeutic dose of alprazolam (difference of LS Means vs placebo: -3.4; $p<0.03$). The anxiolytic effect of JNJ-61393215 was present in most subjects and was driven by a reduction in severity of 9/13 items of the PSL-IV, suggesting a broad anxiolytic effect. The low dose of JNJ-61393215 caused a numerical, statistically non-significant decrease in anxiety symptoms.
Conclusions: JNJ-61393215 90mg showed a statistically significant effect on the PSL-IV total score compared to placebo; a significant anxiolytic effect was also demonstrated for alprazolam at a therapeutic dose.
This study demonstrates for the first time in humans the anxiolytic effects of a selective orexin-1 receptor antagonist and provides supporting rationale to test the efficacy of JNJ-61393215 in a patient population.

TRANSLATIONAL RESEARCH WITH DEXMEDETOMIDINE (DM) FOR THE TREATMENT OF AGITATION FROM HEALTHY VOLUNTEERS TO TWO PATIENT GROUPS: THOSE WITH SCHIZOPHRENIA OR WITH PROBABLE SENILE DEMENTIA OF THE ALZHEIMER'S TYPE (SDAT)

Sheldon Preskorn[1], Rishi Kakar[2], Sammeer Sharma[3], Vincent O'Neill[3], Robert Risinger*[3], *Frank Yocca[3]*
[1]Kansas University School of Medicine, [2]Institute of Neurosciences, Kolkata, [3]BioXcel Therapeutics

Abstract: Background: DM is a highly selective alpha-2 adrenergic agonist currently marketed for intravenous (IV) administration to sedate/anesthetize patients prior to and/or during surgical and other procedures and to sedate intubated and mechanically ventilated patients. Given the role of the central adrenergic system in arousal, DM may be useful for the treatment of agitation in patients with various neuropsychiatric disorders including senile dementia of the Alzheimer's Type (SDAT) and schizophrenia.
Methods: Three identically designed, double-blind, placebo-controlled, randomized studies were conducted with the IV formulation of DM in (a) middle-aged to elderly healthy volunteers (HV), (b) agitated patients with schizophrenia, and (c) agitated patients with SDAT. The DM was administered IV with a starting dose of 0.1 mcg/kg/hour and the dose was increased by 0.1 mcg/kg/hour every 30 minutes up to a maximum dose of 0.6 mcg/kg/hour or until predetermined endpoints were met either for efficacy or safety specifically blood pressure (BP) and heart rate (HR). In the HV, mild sedation was taken as the surrogate for efficacy and measured using the Richmond Agitation Sedation Scale (RASS). The RASS was also used in the studies of agitated patients with either SDAT or schizophrenia. In addition, the PANSS excitatory component (PEC) scale was in the study of agitated patients with schizophrenia. The numbers of participant in each study had 12 – 14 and 4 -6 subjects treated with DM and placebo, respectively. Continuous assessment was made of level of arousal, BP and HR. Plasma samples

were collected before dosing and then every 15 minutes for the determination of DM concentration. Statistics were descriptive and correlational in terms of pharmacodynamic and pharmacokinetic relationships.
Results: Similar results were found in all three studies. DM was capable of producing a light sedation in all subjects (RASS = -1) which was preceded by a calming effect (RASS = 0) in the agitated subjects as well as a reduction in PEC in agitated patients with schizophrenia. These beneficial effects occurred to a greater degree on DM than placebo and before causing clinically meaningful effects on BP or HR. There was an approximately 4-fold variability in the dose and plasma concentration needed to produce these effects in all three groups. The effective dose range was the same across all three groups. The effect occurred within 30 minutes of starting the dose which produced the desired effect. The calming and the drowsy effect persisted for 1.5-2 hours after the cessation of the infusion which was judged to be a clinically relevant duration. Plasma drug concentration correlated with dosing rate and with drug effect both within and between subjects. Gender affected drug responsiveness with males requiring twice the dose of DM compared to females. Additional factors that may account for the difference in dose needed amongst HV and patients include genetic variations in the gene for the alpha-2 adrenergic receptor and sympathetic tome as measured by changes in blood pressure between lying and standing.
Conclusions: This study demonstrated the efficiency of an adaptive, translational design to early phase CNS drug development and is directly relevant to three topics of interest to the Society: Translational Research into Clinical Practice, Patient-focused Drug Development, and Genomics. Using this information, a sublingual film formulation has been developed for further studies.

A COMBINATION OF OLANZAPINE AND SAMIDORPHAN FOR SCHIZOPHRENIA: EFFECTS ON WEIGHT GAIN AND METABOLIC PARAMETERS IN THE PHASE 3 ENLIGHTEN-2 STUDY AND SUBSEQUENT LONG-TERM, OPEN-LABEL SAFETY STUDY

John Newcomer*[1], *Christoph Correll[2], Rene Kahn[3], Bernard Silverman[4], Lauren DiPetrillo[4], Christine Graham[4], Ying Jiang[4], Yangchung Du[4], Adam Simmons[4], Craig Hopkinson[4], David McDonnell[5]*
[1]South Florida Behavioral Health Network, [2]Zucker Hillside Hospital, [3]Icahn School of Medicine at Mount Sinai, [4]Alkermes, Inc., [5]Alkermes Pharma Ireland Ltd.

Abstract: Background: A combination of olanzapine and samidorphan (OLZ/SAM) is in development for schizophrenia. Samidorphan is an opioid receptor antagonist intended to mitigate weight gain and many of the long-term metabolic consequences from olanzapine, while maintaining olanzapine's antipsychotic efficacy. In a prior 4-week study, OLZ/SAM significantly reduced schizophrenia symptoms vs placebo, similar to olanzapine alone. The phase 3 study, ENLIGHTEN-2, extended findings from previous phase 1 and 2 studies and evaluated weight gain with OLZ/SAM vs olanzapine alone over 24 weeks. Here, we report the effects of OLZ/SAM and olanzapine on weight and metabolic parameters from ENLIGHTEN-2. An interim analysis of weight and metabolic data will be presented from an ongoing, long-term, open-label safety extension study.
Methods: This was a phase 3, multicenter, randomized, double-blind study (ClinicalTrials.gov: NCT02694328) in adults 18–55 years of age with stable Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)-diagnosed schizophrenia suitable for outpatient treatment. Eligible patients were randomized 1:1 to once-daily matching OLZ/SAM (10/10 mg) or olanzapine (10 mg) oral tablets. Doses were titrated up to OLZ/SAM 20/10 mg or

olanzapine 20 mg after 1 week (depending on tolerability, could be decreased back to initial dose), and were fixed for the study duration after week 4. Co-primary end points were percent change from baseline (BL) in body weight and proportion of patients with ≥10% weight gain at week 24. Weight, waist circumference, and fasting metabolic laboratory parameters (serum triglyceride [TG], low- and high-density lipoprotein [LDL, HDL], total cholesterol, glucose, and insulin) as well as hemoglobin (Hb) A1c were measured at screening, BL, and throughout the 24 weeks. Upon completion, patients could enroll into the open-label, 52-week safety extension study.
Results: A total of 561 patients were randomized (OLZ/SAM, n=280; olanzapine, n=281); 550 patients received ≥1 dose of study drug, 538 had at least 1 post-BL weight assessment, and 352 (62.7%) completed treatment. The most common reason for discontinuation was adverse events (AEs; 10.9%). BL characteristics were generally similar between groups (mean [SD] age, 40.2 [9.90] years; 73% male; 71% black). Mean (SD) weight at BL was 77.0 (13.7) kg in the OLZ/SAM group and 77.5 (13.5) kg in the olanzapine group. At week 24, least squares (LS) mean (SE) percent change from BL in weight was 4.21 (0.68)% vs 6.59 (0.67)% in the OLZ/SAM vs olanzapine groups, respectively (difference, −2.38 [0.76]%; P=.003). The proportion of patients in the OLZ/SAM and olanzapine groups with ≥10% weight gain was 17.8% vs 29.8% (P=.003; odds ratio [95% CI], 0.50 [0.31–0.80]), respectively. At week 24, LS mean (SE) change from BL in waist circumference was 2.36 cm (0.56) and 4.47 cm (0.55) in the OLZ/SAM and olanzapine groups, respectively (P<.001). No significant differences in metabolic laboratory parameter changes from BL to week 24 were noted between OLZ/SAM and olanzapine alone. Common AEs (≥10%) in the OLZ/SAM and olanzapine group were weight increased (24.8%, 36.2%), somnolence (21.2%, 18.1%), dry mouth (12.8%, 8.0%), and increased appetite (10.9%, 12.3%), respectively.
Discussion: In patients treated with OLZ/SAM, mean percent weight gain was significantly lower, and significantly fewer patients gained ≥10% weight in comparison with olanzapine alone. Metabolic laboratory parameter changes were similar over 24 weeks with OLZ/SAM and olanzapine alone.

FOLLOW-UP ON THE DEVELOPMENT OF KARXT: RESULTS OF KAR-003, A MULTIPLE ASCENDING DOSE (MAD) STUDY OF A COMBINATION PRODUCT

Stephen Brannan*[1], *Andrew Miller*[1], *Steven Paul*[1], *Alan Breier*[2]
[1]*Karuna Pharmaceuticals,* [2]*Indiana University*

Abstract: Background: KarXT is a novel therapeutic consisting of xanomeline plus trospium. A previous Phase I clinical trial demonstrated that the addition of trospium, a peripheral cholinergic receptor antagonist that does not cross the blood brain barrier, to xanomeline substantially improved its tolerability by reducing peripheral cholinergic side effects. We now report the results of a Phase 1, multi-dose safety study aimed at optimizing the KarXT combination of xanomeline with trospium using a new BID co-formulation.
Methods: 69 healthy volunteers participated in the phase 1 multiple ascending dose (MAD) study of KarXT focusing on peripheral cholinergic side effects (nausea, vomiting, diarrhea, excess sweating and salivation), safety and tolerability. The study design was comprised of a 2-day titration period of either placebo or a KarXT dose of 50 mg xanomeline + 20 mg trospium followed by a 5-day treatment period. The doses (all BID) assessed were: xanomeline 100 mg, 125 mg and 150 mg in combination with trospium 20 mg or 40 mg.
Results: The 2-day titration of 50/20 was well tolerated in all cohorts. Cohorts dosing 100 and 125 BID of xanomeline were also well tolerated when paired with 20 mg and 40 mg BID of trospium, respectively. Doses of 150 mg were not well tolerated. Across the cohorts,

cholinergic adverse events (ChAEs) were correlated with xanomeline dose. Increasing trospium dose to 40 mg BID ameliorated ChAEs, and lead to the observance of some anticholinergic adverse events (i.e., dry mouth). Saliva volumes collected corroborated with these findings. The saliva volume of the most affected cohort (125/40) decreased by 1.42 ml relative to baseline, contrasted with placebo which showed a 1.31 ml increase. Most AEs occurred within the first few days of starting or increasing the study drug. The majority of these AEs at 100 mg and 125 mg xanomeline-dose levels were mild and transient in nature. None of the cohorts showed meaningful changes in orthostatic HR or obvious differences in BP between placebo and KarXT compared to placebo. All cohorts receiving KarXT showed placebo-adjusted increases in mean resting HR consistent with past studies with xanomeline where short-term increases in resting HR were observed that normalized to baseline over time. Both trospium and xanomeline exposures (AUCs) and variability were comparable to KAR-001 where the compounds were given using separate formulations.
Conclusions: The new KarXT co-formulation of xanomeline and tropsium performed well in healthy controls and is currently being tested in schizophrenia patients with acute psychosis at 100/20 and 125/30 doses. Longer term studies will provide further data around the safety and tolerability of KarXT, as well as the possible attenuation of AEs over time. No new safety signals were reported in the present study. The timing and duration of AEs were related to peak drug levels (Cmax) and suggest that there is a potential for increased tolerability over time. Importantly, the tolerability observed in this healthy volunteer study may not be representative of schizophrenic patients, who tolerate currently marketed antipsychotic medicines better than healthy volunteers.

AXS-05, ORAL NMDA RECEPTOR ANTAGONIST WITH MULTIMODAL ACTIVITY, IN MAJOR DEPRESSIVE DISORDER: RESULTS OF A PHASE 2, DOUBLE-BLIND, ACTIVE-CONTROLLED TRIAL

Cedric O'Gorman*[1], *Ashley Anderson[1], Mark Jacobson[1], Kellie Kennon[1], Herriot Tabuteau[1]*
[1]Axsome Therapeutics Inc.

Abstract: Background: AXS-05 is a novel, oral, investigational NMDA receptor antagonist with multimodal activity, consisting of dextromethorphan (DM) and bupropion. AXS-05 was evaluated in a Phase 2 trial in major depressive disorder (MDD) and is being evaluated in a Phase 3 trial in treatment resistant depression (TRD). The DM component of AXS-05 is an NMDA receptor antagonist, sigma-1 receptor agonist and inhibitor of norepinephrine and serotonin reuptake. The bupropion component of AXS-05 increases plasma concentrations of DM by inhibiting its metabolism and is a norepinephrine and dopamine reuptake inhibitor. Both DM and bupropion are nicotinic acetylcholine receptor antagonists. The multimodal mechanisms of action of AXS-05 may be complementary and synergistic for MDD.
MDD is a debilitating condition. According to the NIMH, over 16 million U.S. adults experience at least one major depressive episode in a given year. Nearly two-thirds of treated patients with MDD do not experience an adequate response with first-line therapy, and most of these also fail second-line treatment. Time to clinically meaningful response with currently available antidepressants (6-8 weeks) is also suboptimal. There is an urgent need for new, more effective, mechanistically novel MDD treatments.
Objective: To evaluate the efficacy and safety of AXS-05 versus bupropion in MDD.
Methods: The study was a Phase 2, randomized, double-blind, active-controlled, multi-center, U.S. trial, in which 80 adult subjects with a diagnosis of moderate to severe MDD, confirmed by an independent clinical assessor, were treated either with AXS-05 (45 mg DM/105 mg bupropion) (n=43), or the active comparator bupropion (105 mg) (n=37), twice daily for 6

weeks. The primary endpoint was the change from baseline in the MADRS total score, calculated at each study timepoint and averaged (overall treatment effect).
Results: On the primary endpoint, AXS-05 demonstrated a statistically significant mean reduction from baseline in the MADRS total score over the 6-week treatment period of 13.7 points versus 8.8 for bupropion ($p<0.001$). At Week 6, AXS-05 demonstrated a 17.2 point reduction in the MADRS total score compared to a 12.1 point reduction for bupropion ($p=0.013$). AXS-05 rapidly reduced depressive symptoms, demonstrating a statistically significant improvement over bupropion on the CGI-I scale at Week 1 ($p=0.045$). Starting at Week 1, AXS-05 achieved superiority over bupropion on the MADRS total score, with statistical significance achieved at Week 2 and maintained at all time points thereafter. At Week 6, 47% of AXS-05 patients achieved remission (MADRS total score of ≤ 10), compared with 16% of bupropion patients ($p=0.004$). There were no serious adverse events (AEs) and the most commonly reported AEs in the AXS-05 arm were nausea, dizziness, dry mouth, decreased appetite, and anxiety. Treatment with AXS-05 was not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction.
Conclusion: Treatment with AXS-05 resulted in a substantial, rapid, and statistically significant reduction in depressive symptoms, as compared to the active comparator bupropion. AXS-05 was safe and well tolerated in the trial with no reported serious AEs. Based on the rapid and substantial antidepressant effects of AXS-05 as compared to bupropion, its novel NMDA and multimodal mechanisms of action, oral administration, and favorable safety profile, AXS-05 has the potential to address the urgent medical need for new, more effective and mechanistically different antidepressants.

EFFICACY AND SAFETY OF SEP-363856, A NOVEL PSYCHOTROPIC AGENT WITH A NON-D2 MECHANISM OF ACTION, IN THE TREATMENT OF SCHIZOPHRENIA: A 4-WEEK, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Kenneth Koblan*[1], *Seth C. Hopkins*[2], *Justine Kent*[2], *Hailong Cheng*[2], *Robert Goldman*[2], *Antony Loebel*[2]
[1]*Sunovion Pharmaceuticals, Inc.*, [2]*Sunovion Pharmaceuticals, Inc., Marlborough, MA and Fort Lee, NJ*

Abstract: Background: SEP-363856 is a novel psychotropic agent that has shown broad efficacy in animal models of schizophrenia and depression (data-on-file). Its antipsychotic effects appear to be mediated by agonist activity at both trace amine-associated receptor 1 (TAAR1) and 5-HT1A receptors. Notably, SEP-363856 does not bind to any dopaminergic, serotonergic (except 5-HT1A), glutamatergic, or other neuroreceptors thought to mediate the effects of currently available antipsychotics. The aim of this Phase 2 study was to evaluate the efficacy and safety of SEP-363856 in acutely symptomatic patients with schizophrenia.
Methods: Hospitalized patients aged 18-40 years meeting DSM-5 criteria for schizophrenia (PANSS total score ≥ 80) were randomized, double-blind, to 4-weeks of flexible-dose SEP-363856 (50 or 75 mg/d) or placebo. Efficacy measures included the Positive and Negative Syndrome Scale (PANSS) total score (primary), PANSS subscale scores, and the Clinical Global Impressions-Severity (CGI-S) score. Change from baseline in primary and secondary measures were analyzed using a mixed model for repeated measures (MMRM) analysis.
Results: Study treatment groups were similar at baseline: SEP-363856 (N=120; male, 64.2%; mean age, 30.0 years; PANSS total score, 101.4) and placebo (N=125; male, 63.2%; mean age, 30.6 years; PANSS total score, 99.7). Least-squares (LS) mean reduction from baseline to week 4 was significantly greater for SEP-363856 vs. placebo on the PANSS total score (-17.2 vs. -9.7; P=0.001; effect size, 0.45), PANSS positive subscale score (-5.5 vs. -3.9; P=0.019; effect

size, 0.32), PANSS negative subscale score (-3.1 vs. -1.6; P=0.008; effect size, 0.37), PANSS general psychopathology subscale score (-9.0 vs. -4.7; P<0.001; effect size, 0.51), and the CGI-Severity score (-1.0 vs. -0.5; P<0.001; effect size, 0.52). Discontinuation rates for SEP-363856 vs. placebo were similar overall (21.7% vs. 20.8%) and due to an adverse event (8.3% vs. 6.4%). Change in weight, lipids, glucose and prolactin was similar in SEP-363856 and placebo groups. Adverse events occurring with an incidence ≥2% on SEP363-856 or placebo (with SEP363-856 incidence higher than placebo) were: somnolence (6.7% vs. 4.8%), agitation (5.0% vs. 4.8%), nausea (5.0% vs. 3.2%), diarrhea (2.5% vs. 0.8%), and dyspepsia (2.5% vs. 0%). The proportion of patients who reported any extrapyramidal symptom was 3.3% on SEP-363856 and 3.2% on placebo.
Discussion: In this placebo-controlled study, treatment with SEP-363856, a novel psychotropic agent, was associated with statistically significant and clinically meaningful improvement in schizophrenia symptoms as demonstrated by endpoint change in PANSS total and subscale scores, and CGI-Severity scores. Safety and tolerability findings for SEP-363856 were in general similar to placebo. In particular, SEP-363856 was not associated with extrapyramidal symptoms, akathisia, or hyperprolactinemia, consistent with its non-D2 mechanism of action.
ClinicalTrials.gov identifier: NCT02969382

A RANDOMIZED, PLACEBO CONTROLLED, REPEAT DOSE PHASE 1B STUDY OF COR388 IN OLDER HEALTHY VOLUNTEERS AND PATIENTS WITH ALZHEIMER'S DISEASE WITH EXPLORATORY EFFICACY MEASURES

Michael Detke*[1], *Casey Lynch[1], Leslie Holsinger[1], Shirin Kapur[1], Debashish Raha[1], Dave Hennings[1], Mark Ryder[2], Ira Goodman[3], Steve Thein[3], Steve Dominy[1], Florian Ermini[1], Ursula Haditsch[1]*
[1]Cortexyme, [2]UCSF, [3]Pacific Research Network

Abstract: Background: COR388 is a novel bacterial virulence factors inhibitor being developed for the treatment of Alzheimer's disease (AD). The mechanism of action is based on the discovery of Porphyromonas gingivalis (Pg) in the brain and cerebral spinal fluid of AD patients. Toxic virulence factors from the bacterium, called gingipains, were also identified in the brain of AD patients and levels correlated with tau and ubiquitin pathology. Oral infection of mice with Pg resulted in brain colonization, increased production of Aβ1-42, and exerted detrimental effects on tau and loss of hippocampal neurons. Cortexyme designed and synthesized small-molecule gingipain inhibitors to block this neurotoxicity and COR388 was selected to progress to human trials. In a first-in-human single ascending dose study, COR388 was safe and well tolerated from 5 to 250 mg.
Methods: Cohorts 1-3 enrolled 24 healthy volunteers 55-80 years of age, housed in a phase 1 unit, who received 25, 50, and 100 mg (respectively) of COR388 or placebo q12h for 10 days. Cohort 4 enrolled AD subjects 55-85 with baseline MMSE between 14 and 25, screening MRI compatible with AD, and no other cause of dementia, who were allowed to stay on symptomatic treatments for AD. They received 50 mg of COR388 or placebo q12h for 28 days as outpatients. A lumbar puncture was performed on Days 1 and 28.
Results: In cohorts 1-3, 18 subjects received COR388 and 6 received placebo. In cohort 4, 6 received COR388 and 3 received placebo. COR388 was safe and well tolerated in this study. Adverse events were infrequent, transient, and mild-moderate in severity. No SAEs were reported and no patients withdrew from the study due to AEs. No clinically significant trends were seen in laboratory values or ECGs.
COR388 was absorbed rapidly (Tmax = 0.5-1.5 hours) and therapeutic levels in animal models were achieved. COR388 cleared rapidly with a half-life of 4.5-5 hours at steady state. COR388

was detected in human CSF at ratios consistent with that in other species indicating therapeutic CNS levels.
P. gingivalis DNA fragments were detected in the CSF of 9 out of 9 AD subjects analyzed by PCR. MMSE scores on Day 15 and 28 showed a numerical trend of improvement for COR388 compared to placebo. CANTAB measures also showed a numerical trend of improvement for COR388 compared to placebo, on measures of episodic memory, memory composite and psychomotor speed. Winterlight's speech and cognitive battery revealed statistically significant improvements in the COR388 group vs. placebo in total content units (the total number of details present the image), total number of objects (chair, blanket, etc.), and use of prepositions and subordinating conjunctions (to, on, although, because, etc.).
Conclusions: COR388 is a promising drug for the treatment of AD with a novel mechanism of action. COR388 is readily bioavailable after oral administration with a favorable PK profile. COR388 was safe and well tolerated by older subjects and patients with AD when given at doses ranging from 25 to 100 mg BID for up to 28 days. There was a trend of improvement in some of the cognitive tests of the AD patients treated with COR388 HCl in this study, and significant improvement in language tests, however, these results should be interpreted with caution due to the small sample size. Based on these data, Cortexyme is planning to initiate a large phase 2/3 study of COR388 in mild to moderate AD in 2019.

MDMA-ASSISTED PSYCHOTHERAPY FOR TREATMENT OF ANXIETY RELATED TO LIFE-THREATENING ILLNESSES

Allison Feduccia*[1], *Lisa Jerome*[1], *Philip Wolfson*[2], *Michael Mithoefer*[3]
[1]*MAPS Public Benefit Corporation,* [2]*Ketamine Research Foundation,* [3]*Medical University of South Carolina*

Abstract: Background: Before MDMA (commonly known as "Ecstasy") was classified as a Schedule 1 controlled substance in 1985, there were published reports of its use as an adjunct to psychotherapy. However, no controlled research was done at that time. The nonprofit organization the Multidisciplinary Association for Psychedelic Studies (MAPS) sponsored six Phase 2 clinical trials from 2004-2017 using MDMA-assisted psychotherapy for treatment of PTSD. The significant efficacy results and favorable safety profile led the FDA to grant Breakthrough Therapy designation in 2017 for this promising treatment for PTSD. These studies have prompted interest in investigating other anxiety-related conditions that could possibly benefit from MDMA-assisted psychotherapy. Here we present results from a double-blind, randomized Phase 2 trial of MDMA-assisted psychotherapy for anxiety related to life-threatening illnesses (LTI).
Methods: Participants with anxiety from an LTI were randomized in a double-blind study to receive MDMA (125 mg, n=13) or placebo (n=5) during two 8-hour psychotherapy sessions. Non-drug therapy sessions were conducted prior to and after experimental sessions. The primary outcome was change from baseline in State-Trait Anxiety Inventory (STAI) Trait scores at one month post the second experimental session. After the blind was broken, participants in the MDMA group had an additional open-label MDMA session, and placebo participants crossed over to receive three open-label MDMA sessions. The treatment period lasted from 4-6 months with long-term follow-up assessments six and twelve months after the final MDMA session.
Outcomes: For the primary outcome, the MDMA group had the largest mean (SD) drop in STAI-Trait scores -23.5 (13.2) indicating less anxiety compared to placebo group -8.8 (14.7), with results trending towards significant group differences (p=0.056). Cohen's d between group effect size was 1.7 (CI: -0.30, 3.65), indicating a large treatment effect. At the six- and

twelve-month follow-ups, most domains of psychological functioning were markedly improved compared to baseline, including anxiety (STAI State and Trait, $p<0.0001$), depression (BDI-II and MADRS, $p<0.0001$), sleep quality (PSQI, $p<0.001$), and global functioning ($p<0.001$). MDMA was well-tolerated in this population with a good safety profile in terms of adverse event rates and transient increases in vital signs after MDMA administration.
Conclusion: Few treatments available adequately address psychological symptoms that often accompany physical illnesses. Initial safety and efficacy data from this pilot study support the expansion of clinical trials of MDMA-assisted psychotherapy into a larger sample of individuals with anxiety associated with life-threatening illnesses.
Funding: Multidisciplinary Association for Psychedelic Studies (MAPS)
Trial Registration: clinicaltrials.gov Identifier: NCT02427568

PATIENT SATISFACTION WITH INJECTABLE WEEKLY AND MONTHLY BUPRENORPHINE AND BUPRENORPHINE TREATMENT EXPERIENCE

Genie Bailey[1], Michael Frost[2], Sonnie Kim[3], Natalie Budilovsky-Kelley*[3], *Fredrik Tiberg[4]*
[1]Brown University, Human Behavior and Stanley Street Treatment and Resources, Inc, [2]Frost Medical Group, [3]Braeburn, [4]Camurus

Abstract: Interventions addressing opioid use disorder (OUD) are often evaluated by objective measures including treatment retention, illicit opioid use, and morbidity/mortality. These criteria, though important, do not necessarily reflect patient priorities. Patient satisfaction is viewed as an important healthcare outcome and has been used as a measure of quality of care. The relationship between patient satisfaction and healthcare outcomes is not straightforward, however, evidence suggests that patient satisfaction is a signal for positive outcomes in OUD treatment.
Long-term safety, tolerability and efficacy of a weekly and monthly extended-release injectable buprenorphine (CAM2038) was evaluated in a 48-week, open-label, multi-center, multi-national study in adults with moderate-to-severe OUD. New entrants to treatment were initiated with CAM2038 weekly and after stabilization, could be transitioned to CAM2038 monthly. Individuals receiving sublingual buprenorphine +/- naloxone (SL BPN) at baseline were converted to a corresponding dose of CAM2038 weekly or monthly, and then were maintained on CAM2038 weekly or monthly. Dose adjustments and transitions between CAM2038 weekly and monthly were individualized in accordance with clinical needs. At months 6 and 12, participants in both groups completed a non-validated survey to evaluate patient satisfaction with CAM2038 and experience regarding BPN treatment for OUD. To evaluate satisfaction with CAM2038 at month 12, participants who converted from SL BPN were asked to evaluate their overall experience with CAM2038 as compared to their pre-study SL BPN on a 5-unit scale from "much worse" to "much better". To evaluate BPN treatment experience, participants in both groups were asked to rate the importance of 7 characteristics regarding BPN treatment for OUD, in general, on a scale of 1-7, where 1 was "not important" and 7 was "extremely important". Items addressed were ease of travel, daily compliance, privacy, need for daily medication and trips to the pharmacy, accidental pediatric exposure, and access for others to medications.
167 participants completed the treatment period; 29 (17%) in the new to treatment (NTT) group and 138 (83%) in the conversion from SL BPN group. 110 surveys were completed month 6, 34 by the NTT group and 76 by the conversion group. 162 surveys were completed month 12, 29 by the NTT group and 133 by the conversion group. For patient satisfaction at month 12, of the 133 responding participants who converted from SL BPN to CAM2038, 91 (68.4%)

answered that treatment with CAM2038 was “much better” than their previous BPN treatment, 20 (15%) answered that it was “slightly better”, 9 (6.8%) responded that CAM2038 was “slightly worse” and 4 (3.0%) responded that CAM2038 was “much worse”. 1 of the 4 participants who responded treatment with CAM2038 was “much worse” experienced an adverse event (AE) of moderate or greater severity. This AE was a migraine headache of moderate severity assessed by the principal investigator to be “possibly” related to investigational product. For BPN treatment experience, at 6 and 12 months, the median score (in both groups) across the outlined characteristics of their BPN treatment was 7.0 (extremely important) for all items except for a median score of 6.5 for “prevents others access to my medication” at month 6 for the NTT group.
Participants reported high levels of satisfaction with treatment provided by weekly/monthly CAM2038. Participants found ease of travel, supported daily adherence, improved privacy, lack of need for daily medication or regular trips to pharmacy, prevention of accidental pediatric exposure and access by others to medications as important characteristics of BPN treatment.

SNAP 101: RANDOMIZED, CROSSOVER, ACTIVE AND PLACEBO-CONTROLLED, SAFETY, PHARMACOKINETIC, AND PHARMACODYNAMIC STUDY OF THREE ASCENDING DOSES OF INP105 - NOVEL PRECISION OLFACTORY DELIVERY (POD) OF A NASAL FORMULATION OF OLANZAPINE

Jasna Hocevar-Trnka*[1], *Stephen Shrewsbury*[1], *Kelsey Satterly*[1], *Meghan Swardstrom*[1]
[1]*Impel NeuroPharma*

Abstract: Objectives: 1) Establish safety and tolerability of three doses of INP105 (POD-olanzapine) 2) Compare PK data for olanzapine (OLZ) from 3 INP105 doses to OLZ IM (5 mg and 10 mg) and orally disintegrating tablets (OLZ-ODT, 10 mg) 3) Compare PD effects of INP105 to OLZ IM, OLZ-ODT and placebo.
Background: An estimated 1.7 million acute agitation events occur annually in US emergency room settings often from serious underlying psychiatric conditions such as bipolar I disorder or schizophrenia; OLZ IM is a preferred option due to a shorter Tmax than oral. However, IM administration, predominantly administered in a hospital setting, can be painful, traumatic, invasive, and requires cooperation or restraint which reduces trust and increases healthcare worker injuries. Further, heavily medicated patients may require “boarding” until sedative effects have resolved. Oral administration of OLZ is preferred but has a slower onset of effect and typically requires isolation and observation of the patient. INP105 is a drug-device combination product in development which delivers a novel powder formulation of OLZ by the Precision Olfactory Delivery (POD®) device to the vascular rich upper nasal space. It is being developed for rapid control of agitation either by self or caregiver administration to provide rapid onset of relief without a needle. INP105 may also be suitable for early use by patients who have insight into their condition and recognize early symptoms of agitation in the home setting. This may avoid escalating agitation leading to more intensive management, violence, and injury to the patient, their caregivers and/or healthcare workers.
Methods: Randomized, double-blind, active and placebo-controlled, single ascending-dose, 2-way, 2 period, crossover Phase 1 trial to compare the safety, tolerability, PK and PD of 3 doses of INP105 (5 mg, 10 mg and 15 mg) or POD-placebo with either OLZ IM (5 mg or 10 mg) or OLZ-ODT (10 mg) in NHVs. Period 1 was open label (the OLZ 10 mg IM dose was discontinued after dosing 2 NHVs); followed by a 14-day washout period and then a double-blind period with INP105 or POD-placebo. Dose escalation was staggered to allow safety monitoring committee assessment of tolerability of INP105 between dose levels. PK draws and

PD assessments (VAS, ACES and DSST), were obtained at multiple timepoints. All subjects were observed as in-patients for at least 72 hours post-dosing with follow-up occurring 4, 5 and 14 days after dosing in both periods.
Results: 40 subjects were randomized; 37 dosed in Period 2 (Placebo=10, INP105 5 mg =10, 10 mg=9, 15 mg=8). INP105 was well tolerated with TEAEs reported in 100% IM OLZ 10 mg, 90% IM OLZ 5 mg, 83.3% OLZ ODT 10 mg, and 70% INP105 5 mg, 60% INP105 10 mg, and 55.6% INP105 15 mg. INP105 was rapidly absorbed with median Tmax of ~10 min, compared to 20 min for IM (both 5 mg and 10 mg doses) and ~120 min for OLZ ODT. Dose-related, statistically significant PD effects with VAS, ACES and DSST were observed for all three INP105 dose levels compared to placebo.
Conclusions: This study demonstrated that Tmax for nasally administered INP105 was twice as fast as IM and 12 times faster than OLZ ODT with a comparable Cmax and AUC to the corresponding IM dose of OLZ. INP105, OLZ delivered by the POD device to the upper nasal cavity, is a needle-free, rapidly available investigational product with potential application in the management of acute agitation.

Individual Research Reports: Broad Spectrum Use of Neuroleptic Agents: Benefits and Liabilities*
4:15 p.m. - 5:30 p.m.

ENHANCING COMPLETION OF COGNITIVE PROCESSING THERAPY FOR POSTTRAUMATIC STRESS DISORDER WITH QUETIAPINE IN VETERANS WITH MILD TRAUMATIC BRAIN INJURY: A CASE SERIES*

Muhammad Baig*[1], *John Roache*[2]
[1]*South Texas Veterans Healthcare System/University of Texas Health Science Center at San Antonio,* [2]*University of Texas Health Science Center at San Antonio*

Abstract: Importance: Mild traumatic brain injury (mTBI) is a signature wound in post-9/11Veterans. Most Veterans have a concurrent diagnosis of posttraumatic stress disorder (PTSD) that results in diagnostic challenges given the overlap of symptoms with mTBI. Unremitted PTSD interferes with rehabilitation outcomes and leads to persistent post-concussive symptoms and impaired functioning.
The limited efficacy of psychopharmacological treatments for comorbid combat-related posttraumatic stress disorder has led to the practice of using multiple medications that still fail to achieve remission while adding the burden of undesired side effects from polypharmacy, which also exacerbate symptoms of mild traumatic brain injury. Trauma-focused psychotherapies have the most robust evidence-bases but are limited by premature dropouts and residual posttraumatic stress disorder symptoms.
Objectives: To evaluate the effects of anti-arousal medications such as valproate, risperidone, or quetiapine on completion of treatment of cognitive processing therapy for posttraumatic stress disorder.
Design: A case series to evaluate the use of anti-arousal medications to facilitate cognitive processing therapy for the treatment of posttraumatic stress disorder in Veterans with mild traumatic brain injury who were resistant to cognitive processing therapy.
Setting: The psychiatric outpatient services of the San Antonio Polytrauma Rehabilitation Center from January 1, 2014, through December 31, 2017.

Participants: 50 treatment seeking adult (≥ 18 years) Veterans with mild traumatic brain injury and combat-related PTSD who had failed trials of two or more first-line agents and previously declined treatment with trauma-focused therapy.
Intervention: Patients were prescribed valproate (N=8), risperidone (N=17), or quetiapine (N=25) and were referred for individual weekly treatment with cognitive processing therapy.
Main Outcomes: Outcome measurements of interest were measures of engagement and completion rate of cognitive processing therapy, PTSD Checklist total score and arousal subscale score, and clinical observations of sleep variables.
Results: 18 (86%) patients taking quetiapine and 0 (0%) taking valproate or risperidone became adequately engaged in cognitive processing therapy. 18 (86%) patients taking quetiapine and 0 (0%) taking valproate or risperidone completed cognitive processing therapy. Among patients who completed cognitive processing therapy, the mean decrease in PTSD Checklist score was 25 [95% CI, 30 to 20] and 9 (50%) patients no longer met criteria for posttraumatic stress disorder.
Conclusions and Relevance: These preliminary findings support quetiapine as an adjunctive medication to facilitate cognitive processing therapy. We suggest the need for a pragmatic trial to evaluate the efficacy, safety, and feasibility of quetiapine to improve engagement and completion rate of cognitive processing therapy.

Learning Objectives:

1. To evaluate anti-arousal medication treatment preliminary data to support hypothesis that quetiapine monotherapy can facilitate rehabilitation for Veterans with PTSD and mTBI by enhancing engagement and completion rate of CPT treatment for PTSD.
2. It can do so without the complications of other standard of care polypharmacy practice.

Literature References:

1. Krystal JH, Davis LL, Neylan TC, M AR, Schnurr PP, Stein MB, et al. It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group. Biol Psychiatry. 2017.
2. Villarreal G, Hamner MB, Canive JM, Robert S, Calais LA, Durklaski V, et al. Efficacy of Quetiapine Monotherapy in Posttraumatic Stress Disorder: A Randomized, Placebo-Controlled Trial. Am J Psychiatry. 2016;173(12):1205-12.

CARIPRAZINE EFFICACY IN PATIENTS WITH BIPOLAR DEPRESSION AND CONCURRENT MANIC SYMPTOMS: POST HOC ANALYSIS OF 3 RANDOMIZED, PLACEBO-CONTROLLED STUDIES*

Trisha Suppes*[1], *Stephen Stahl*[2], *Willie Earley*[3], *Mehul Patel*[3], *Roger McIntyre*[4]
[1]*Stanford University,* [2]*VA Palo Alto Health Care System,* [3]*Allergan,* [4]*Toronto Western Research Institute*

Abstract: Background: Cariprazine, a dopamine D3 preferring D3/D2 receptor and serotonin 5-HT1A receptor partial agonist, is approved for the treatment of schizophrenia (1.5-6 mg/d) and bipolar mania (3-6 mg/d) in adults. Cariprazine has demonstrated efficacy vs placebo (PBO) in 3 phase 2/3 studies of patients with bipolar depression (NCT01396447, NCT02670538, NCT02670551)(1,2). These analyses investigated the efficacy of cariprazine in patients with bipolar depression and concurrent manic symptoms (mixed features).
Methods: Data were pooled from 3 randomized, double-blind, PBO-controlled trials in patients with bipolar I disorder and a current major depressive episode. Concurrent baseline manic symptoms were identified using a Young Mania Rating Scale total score cutoff ≥4. Efficacy outcomes were assessed for cariprazine 1.5 mg/d and 3 mg/d groups vs PBO and included least

squares (LS) mean change from baseline to week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score, Hamilton Depression Rating Scale (HAMD17) total score, and Clinical Global Impressions-Severity (CGI-S) score, analyzed using mixed-effects model for repeated measures. MADRS response (≥50% improvement), MADRS remission (total score ≤10), and CGI-S remission (score ≤2) were analyzed using logistic regression with last observation carried forward.
Results: A total of 808 (58.4%) of 1383 patients had bipolar depression and concurrent manic symptoms. For MADRS score change, the LS mean difference (LSMD) vs PBO was statistically significant in favor of cariprazine 1.5 mg (-2.5, P=.0033) and 3 mg (-2.9, P=.0010) in patients with manic symptoms and for cariprazine 1.5 mg (3.3, P=.0008) in patients without manic symptoms. Similarly, the LSMD vs PBO for HAMD17 total score change was significant for cariprazine 1.5 and 3 mg (-1.9 and -1.5; P<.05 both) in patients with manic symptoms and for cariprazine 1.5 mg (-2.2, P=.0042) in patients without manic symptoms. On CGI-S score change, the LSMD vs PBO was significantly greater for cariprazine 1.5 and 3 mg, respectively, in patients with manic symptoms (-0.24 and -0.25; P<.05 both) and in patients without manic symptoms (-0.40 and -0.26; P<.05 both). Rates of MADRS response and remission, respectively, were significantly greater for cariprazine 1.5 mg (46.6% and 31.3%; P<.05 both) and 3 mg (49.8% and 31.4%; P<.01 both) than PBO (37.8% and 21.0%) in patients with manic symptoms and for cariprazine 1.5 mg (45.2% and 32.3%; P<.05 both) vs PBO (33.3% and 20.7%) in patients without manic symptoms. Rates of CGI-S remission were significantly greater than PBO for all cariprazine doses in both patient subgroups (P<.05 all).
Conclusion: In a post hoc analysis of data from patients with bipolar depression and concurrent manic symptoms, significant improvement in depressive symptoms was demonstrated for cariprazine vs PBO, suggesting that cariprazine may be an appropriate treatment option for this patient population.

Learning Objectives:

1. At the conclusion of this session, participants will be able to recognize the benefit of treating patients with bipolar depression and concurrent manic (mixed) symptoms.
2. At the conclusion of this session, participants will be able to describe the improvements in depressive symptoms observed with cariprazine treatment in patients with bipolar depression and concurrent manic symptoms.

Literature References:

1. Durgam S, Earley W, Lipschitz A, et al: An 8-Week Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients With Bipolar I Depression. Am J Psychiatry 2016;173:271-281.
2. Earley W, Burgess M, Khan B, et al: Treatment of Bipolar I Depression with Cariprazine: A Randomized Double-Blind Placebo-Controlled Trial. Presented at Psych Congress. Orlando, FL, USA; October 25-28, 2018.

MORBIDITY AND MORTALITY OF MEDICATIONS USED TO TREAT INSOMNIA: CASES REPORTED TO U.S. POISON CONTROL CENTERS 2000-2016*

J. Craig Nelson*[1], *Matthew Noble*[2], *Daniel A. Spyker*[3]
[1]*University of California San Francisco,* [2]*Oregon Health & Science University,* [3]*Oregon Poison Control Center, Oregon Health and Science University*

Abstract: Objective: Insomnia is a common problem worldwide and prescriptions for sedatives and hypnotics continue to rise. Deaths from suicide, particularly those associated with medication ingestion, have risen steadily in the US during the past 17 years and sedatives and hypnotics are among those showing the greatest increase. The objective of this study was to examine the relative morbidity and mortality of medications used to treat insomnia.

Methods: The American Association of Poison Control Centers' National Poison Data System (NPDS) contains reports from regional poison centers serving 50 States and US territories. NPDS was queried for single drug exposures in individuals 12 years and older during the period 2000-2016, for 42 medications used for insomnia. Outcomes analyzed were the Morbidity Index = number of serious outcomes per 1,000 exposures, and the Mortality Index = number of fatal outcomes per 10,000 exposures.
Results: During this 17-year period there were 876,662 single substance exposures for the 42 medications studied and serious outcomes rose 3.2-fold. Morbidity and mortality indices varied widely. Among the commonly ingested medications, amitriptyline and doxepin had very high morbidity and mortality indices. Quetiapine and olanzapine had relatively high indices. Although the lower doses of these agents used for insomnia may be safe in limited quantities, the data suggest that a substantial portion of ingestions are large amounts. Although there were statistically significant differences between indices for the benzodiazepines and z-drugs, these differences were small relative to the wide range of indices found.
Conclusions: Serious outcomes after ingestions of medications used for insomnia have risen substantially between 2000 and 2016. The morbidity and mortality indices of these medications vary widely. Clinicians should consider the safety of medications when selecting a treatment for insomnia.

Learning Objectives:

1. At the conclusion, the participant will be able to describe the hypnotics associated with high morbidity and mortality.
2. The participant will be able identify the limitations of the study.

Literature References:

1. Gummin DD, Mowry JB, Spyker DA, et al. 2016 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th Annual Report. Clin Toxicol (Phila). 2017; 55(10):1072-1252.
2. Nelson JC, Spyker DA. Morbidity and Mortality Associated With Medications Used in the Treatment of Depression: An Analysis of Cases Reported to U.S. Poison Control Centers, 2000-2014. Am J Psychiatry. 2017;174(5):438-450.

C-REACTIVE PROTEIN AND RESPONSE TO LURASIDONE TREATMENT IN CHILDREN AND ADOLESCENTS WITH BIPOLAR DEPRESSION*

Andrei Pikalov*[1], *Charles Raison[2], Cynthia Siu[3], Michael Tocco[1], Antony Loebel[4]*
[1]Sunovion Pharmaceuticals, Inc., [2]University of Wisconsin-Madison, [3]COS & Associates Ltd., [4]Sunovion Pharmaceuticals, Inc., Fort Lee, NJ and Marlborough, MA

Abstract: Objective: In a short-term clinical trial of adults with bipolar depression randomized to receive flexibly dosed lurasidone (20-120 mg/d) or placebo, lurasidone-treated patients with high baseline CRP levels demonstrated a larger treatment effect compared to patients with lower baseline CRP levels.1 The current analysis explores the association between high-sensitivity CRP (hsCRP) levels prior to treatment, depressive symptoms, and cognition in a short-term, placebo-controlled clinical study of lurasidone in children and adolescents with bipolar depression.
Methods: Patients 10-17 years of age with a DSM-IV-TR diagnosis of bipolar I depression, were randomized to 6 weeks of double-blind treatment with flexibly dosed lurasidone 20-80 mg/d or placebo. The primary efficacy measure was the change from baseline to week 6 in the Children's Depression Rating Scale, Revised (CDRS-R). Treatment response was defined as 50% or greater improvement on the CDRS-R from baseline to week 6. Cognitive function was evaluated with the computerized Brief Cogstate Battery at baseline and week 6. Baseline BMI,

as well as age, gender and race were adjusted in the analysis. The percentiles for the BMI categories were derived based on the WHO 2007 growth reference for 5 to 19 years old. HsCRP was evaluated as a logarithmically transformed continuous variable and as a categorical variable dichotomized into lower (< 1 mg/L) and higher (> 1 mg/L) subgroups. Statistical interaction tests were applied to evaluate whether baseline hsCRP is associated with differential response to lurasidone treatment (vs. placebo) on measures of depressive symptoms and cognitive function.

Results: A total of 248 patients (74%) had a baseline hsCRP serum concentration < 1 mg/L. A significant statistical interaction was found between baseline hsCRP and treatment group for change in CDRS-R score at study endpoint, with larger placebo-corrected effect sizes for lurasidone in the higher baseline hsCRP group (> 1 mg/L). Among patients with higher baseline hsCRP levels, a significant BMI-by-stratified hsCRP-treatment interaction was found, with larger response to lurasidone (i.e. 50% reduction in CDRS-R score) in normal BMI range patients (NNT=1.8) compared to overweight/obese patients (NNT=5.2). Similarly, a significant interaction effect for the combination of hsCRP and BMI on the cognitive effect of lurasidone was found, with higher baseline hsCRP levels associated with improvement in cognitive function for lurasidone (vs placebo) in the normal BMI range subgroup but not in the overweight/obese patients.

At baseline, overweight and obese range BMI was significantly associated with higher levels of hsCRP and CDRS-R total score but not with the cognitive composite score. Associations between hsCRP, CDRS-R, and cognitive performance were not significant at study baseline.

Conclusion: Greater improvement in depressive symptoms and cognitive impairment was observed in young normal-weight patients with bipolar depression and higher levels of hsCRP at study baseline.

Learning Objectives:

1. At the conclusion of this session, the participant will be able to gain further understanding on the antidepressant and cognitive efficacy of lurasidone in young normal-weight patients with bipolar depression and higher levels of hsCRP at study baseline.
2. At the conclusion of this session, the participant will be able to gain further understanding on the influence of inflammation, obesity and lipid metabolism on changes in symptom severity and cognition in children and adolescents with bipolar depression treated with lurasidone.

Literature References:

1. Raison CL, Pikalov A, Siu C, Tsai J, Koblan K, Loebel A. C-reactive protein and response to lurasidone in patients with bipolar depression. Brain, Behavior, and Immunity, 2018; 73:717-724.
2. DelBello MP, Goldman R, Phillips D, Deng L, Cucchiaro J, Loebel A. Efficacy and safety of lurasidone in children and adolescents with bipolar I depression: a double-blind, placebo-controlled study. J Am Acad Child Adolesc Psychiatry, 2017;56:1015-1025.

Individual Research Reports: Biomarkers for Depression: Subtypes and Response to Treatment*

4:15 p.m. - 5:30 p.m.

THE ASSOCIATION BETWEEN BODY MASS INDEX AND REMISSION RATES IN PATIENTS WITH TREATMENT-RESISTANT DEPRESSION WHO RECEIVED INTRAVENOUS KETAMINE*

Balwinder Singh*[1], *William Bobo*[1], *Keith Rasmussen*[1], *Cynthia Stoppel*[1], *Jose Rico*[1], *Kathryn Schack*[1], *Joanna Biernacka*[1], *Mark Frye*[1], *Jennifer Vande Voort*[1]
[1]*Mayo Clinic*

Abstract: Background: Few studies have evaluated optimal dosing of IV ketamine for treatment-resistant depression (TRD). Preliminary studies identified an association between BMI and ketamine response with 0.5 mg/kg infused over 40 minutes. We completed two open-label racemic ketamine trials in TRD patients infused intravenously, 0.5 mg/kg actual body weight, over 100 minutes (1,2). We conducted a secondary analysis from these studies to assess association between BMI and ketamine response at a slower infusion rate.
Methods: We combined subject-level data from two open-label clinical trials of adjunctive IV ketamine for adults with treatment-resistant depression. Treatment resistance was defined on the basis of failure to respond to at least two adequate trials of antidepressive treatment, including medications, ECT or TMS. BMI was analyzed as a continuous and categorical predictor variable (normal, overweight, and class-I and –II obesity). Subjects received multiple infusions (twice weekly up to 4 infusions or thrice weekly up to 6 infusions) until remission was achieved or a maximum number of infusions was administered. Remission was defined as Montgomery-Asberg Depression Rating Scale (MADRS) score of ≤9 at 24 hours post-infusion.
Statistical Analysis: Logistic regression was used to estimate the association between BMI and remission. Based on small sample size, Cochran-Armitage trend test was utilized to evaluate BMI obesity categories (step-wise increases from normal BMI through class II obesity) and remission. JMP Pro 13.0.0 statistical software (SAS Institute, Cary, NC) was used for the analysis.
Results: The combined dataset consisted of 22 depressed subjects who were middle-aged (mean 46.4±11.5 years) and predominantly female (77%), with mean BMI 30.7±6.6. Mean (standard error) change in MADRS score was -16.2±2.8 ($p<0.0001$), a significant reduction (improvement) from baseline (31.2±1.5).
There was a trend association of baseline BMI and remission (OR, 1.17, 95% CI 0.98-1.39, $p=0.07$). When data were arranged in BMI categories, there was a significant association between higher BMI category and remission (83% in obesity class-II, 40% in obesity class-I, 33% in overweight, and 20% in normal weight patients respectively, $p=0.03$).
Importance: This data shows a relationship between baseline BMI and odds of remission, and effect modification of the relationship between ketamine and remission by BMI category. These data have implications when evaluating merits of actual vs ideal body weight in ketamine dosing. Further consideration may be needed before dosing patients based on ideal body weight, as the risk for underdosing this population may exist. This raises an important clinical question that needs further investigation.

Learning Objectives:

1. Evaluate efficacy of adjunct intravenous ketamine for treatment-resistant depression.
2. Evaluate an association between body mass index and remission rates in patients with treatment-resistant depression who received intravenous ketamine.

Literature References:

1. Vande Voort JL, Morgan RJ, Kung S, et al. Continuation phase intravenous ketamine in adults with treatment-resistant depression. Journal of affective disorders 2016;206:300-4.
2. Rasmussen KG, Lineberry TW, Galardy CW, et al. Serial infusions of low-dose ketamine for major depression. Journal of psychopharmacology 2013;27:444-50.

THE EFFECT OF PHARMACOGENOMIC TESTING ON RESPONSE AND REMISSION RATES IN THE ACUTE TREATMENT OF MAJOR DEPRESSIVE DISORDER: A META-ANALYSIS*

Joshua Rosenblat*[1], *Yena Lee*[2], *Roger S. McIntyre*[2]
[1]*University of Toronto,* [2]*University Health Network, University of Toronto*

Abstract: Background: Pharmacogenomic testing has recently become scalable and available to guide the treatment of major depressive disorder (MDD). The objective of the current updated meta-analysis was to determine if guidance from pharmacogenomic testing results in relatively higher rates of remission and response compared to treatment as usual (i.e. 'unguided' trial-and-error method) in adults with MDD.
Methods: Article databases were systematically searched from inception to January 27, 2019 for human studies assessing the clinical utility of pharmacogenomics in the acute treatment of MDD. Treatment outcomes in MDD may be defined continuously or categorically (i.e. response/remission). Herein, we delimit our focus on categorical outcomes. Using a random-effects model, data was pooled to determine the risk ratio (RR) of response and remission, respectively, in the pharmacogenomic-guided treatment group compared to the unguided group. Study quality was also systematically assessed as per the recommendations of the Cochrane Handbook for Systematic Review of Interventions.
Results: Six randomized controlled trials (RCTs; variable blinding) and two open-label, controlled cohort studies were included. The pooled RR for treatment response comparing guided versus unguided treatment was 1.37 (95% confidence interval [CI]=1.21 to 1.54; $p<0.0001$; n=2,066) in favour of guided treatment. The pooled RR for remission was 1.64 (95%CI=1.23 to 2.19; $p=0.0007$, n=2,002) also in favour of guided treatment. Heterogeneity in study results suggest that different genetic tests may variably impact response and remission rates.
Limitations: The available evidence is limited, with significant methodological deficiencies, including inadequate participant blinding, potentially resulting in improved response/remission rates from expectancy bias (e.g., participants in the guided group having improved outcomes from being told they are receiving 'personalized' treatment). Significant reporting bias and funding bias was also identified in most studies.
Conclusion: The current analysis provides preliminary support for improved response and remission rates in MDD when treatment is guided by pharmacogenomics. However, due to significant study limitations, future well designed, adequately blinded RCTs are required to accurately determine the clinical utility of pharmacogenomic-guided antidepressant selection.

Learning Objectives:

1. Evaluate the evidence for improved clinical outcomes with pharmacogenomic-guided antidepressant selection compared to treatment as usual.
2. Discuss the limitations of the currently available evidence for pharmacogenomic-guided antidepressant selection.

Literature References:

1. Rosenblat JD, Lee Y, McIntyre RS: Does Pharmacogenomic Testing Improve Clinical Outcomes for Major Depressive Disorder? A Systematic Review of Clinical Trials and Cost-Effectiveness Studies. J Clin Psychiatry 2017; 78:720–729
2. Rosenblat JD, Lee Y, McIntyre RS: The effect of pharmacogenomic testing on response and remission rates in the acute treatment of major depressive disorder: A meta-analysis. J Affect Disord 2018; 241:484–491

PREDICTION OF ANTIDEPRESSANT TREATMENT OUTCOMES WITH ULTRA-HIGH FIELD MAGNETIC RESONANCE IMAGING*

Christoph Kraus*[1], *Rene Seiger[1], Daniela M. Pfabigan[2], Ronald Sladky[2], Auer Bastian[2], Martin Tik[3], Katharina Paul[2], Michael Woletz[3], Marie Spies[1], Gregor Gryglewski[1], Thomas Vanicek[1], Arkadiusz Komorowski[1], Siegfried Kasper[1], Claus Lamm[2], Christian Windischberger[3], Rupert Lanzenberger[1]*

[1]Medical University of Vienna, [2]University of Vienna, [3]Center for Medical Physics and Biomedical Engineering, Medical University of Vienna

Abstract: Introduction: Structural and functional magnetic resonance imaging (sMRI/fMRI) has successfully discerned neuroanatomical substrates of major depressive disorder (MDD). In addition, assessment and prediction of treatment response with high-field (3T) fMRI yielded anterior cingulate, frontal and amygdalar activity as candidates for response prediction. However, previous studies did not yield sensitivities and specificities high enough to translate fMRI-findings into clinical settings(1, 2). Ultra-high field (7T) fMRI exhibits higher a special resolution and increased BOLD-signal strengths, potentially leading to advantages in antidepressant response prediction (3). We hence conducted a 7T antidepressant fMRI study and aimed to predict response and remission before treatment (at MRI-1).

Methods: We conducted a longitudinal, open-label, flexible-dose antidepressant treatment study with first line treatments (escitalopram-max. 20 mg) and an option to switch to second-line venlafaxine (max. 150 mg) upon non-response after 6 or 8 week-long treatment. 7T structural (MP2RAGE, 32-channel head coil, TR/TE=4060/3.02 ms, voxel x/y/z = 0.74 × 0.68 × 0.68 mm) and functional (multiband, TR/TE=1400/23 ms, voxel x/y/z = 1.5 × 1.5 × 1.0 mm, multiple paradigms) MRI was performed twice; 1 pretreatment scan and another after 12 weeks treating acute patients. In total 29 acute depressed subjects with MDD and as controls 39 stable remitted subjects and 38 healthies finished the protocol. In an electrical painful stimulation paradigm, we modelled 'dynamic response' to antidepressant treatment with a sigmoid function and compared pretreatment with post-treatment with a linear regression analysis. Moreover, we compared baseline and posttreatment hippocampal subfield volumes with a repeated measures ANOVA.

Results: In acute depressed patients (n=26) we found pretreatment elevated activity in the right temporoparietal junction significantly predicting remitter from non-remitter (t=4.1, FWE p=0.005). This cluster had an accuracy of 58%, sensitivity of 41.6% and specificity of 71.4%. Difference between fMRI-1 and fMRI-2 (i.e. treatment effects) between remitter and non-remitter were associated with significantly increased activation in the left orbitofrontal cortex (t=4.7, FWE p=0.034; accuracy=54%, sensitivity=50%, specificity=57%).

Moreover, we did not detect longitudinal hippocampal subfield changes in treated acute depressed patients compared to pretreatment and control groups (interaction group×time F=2.99, p=0.05, no post-hoc tests significant). We found a significant effect of remission status (n=20, F=15.24, p<0.001), as well as a significant interaction of remission×time (F=8.14, p=0.004)n the right fimbria (MRI-1: t=2.8, pTukey =0.037, d=0.19), in the right presubiculum (MRI-1, t=2.55, puncorr =0.011, d=0.17) and in the right fissure (MRI-1: t=2.51, puncorr =0.012, d=0.17).

Conclusions: With 7T fMRI imaging, task-based and hippocampal subfield analysis we detected significant differences between remitter and non-remitter to first-line antidepressant treatments. The results show that structural and functional MRI at 7T is able to distinguish remitter from non-remitter in brain areas known to be affected by MDD. Yet, accuracies of distinguishing remitter from non-remitter of our results are just above chance. In conclusion, it

might be advantageous to increase sample-sizes in longitudinal, pooled studies at widely available lower field-strengths to assess response prediction with MRI.

Learning Objectives:

1. Learn how hippocampal subfield volumes change according to antidepressant treatment.
2. Advantages and Disadvantages of 7T Imaging in longitudinal antidepressant trials.

Literature References:

1. Williams LM, Korgaonkar MS, Song YC, Paton R, Eagles S, Goldstein-Piekarski A, Grieve SM, Harris AW, Usherwood T, Etkin A. Amygdala Reactivity to Emotional Faces in the Prediction of General and Medication-Specific Responses to Antidepressant Treatment in the Randomized iSPOT-D Trial. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2015;40:2398-2408.
2. Gyurak A, Patenaude B, Korgaonkar MS, Grieve SM, Williams LM, Etkin A. Frontoparietal Activation During Response Inhibition Predicts Remission to Antidepressants in Patients With Major Depression. Biological psychiatry. 2016;79:274-281.
3. Hahn A, Kranz GS, Seidel EM, Sladky R, Kraus C, Kublbock M, Pfabigan DM, Hummer A, Grahl A, Ganger S, Windischberger C, Lamm C, Lanzenberger R. Comparing neural response to painful electrical stimulation with functional MRI at 3 and 7 T. NeuroImage. 2013;82:336-343.

EFFECT OF LIFETIME HISTORY OF A SUBSTANCE USE DISORDER IN ESTABLISHING BIOMARKERS IN MAJOR DEPRESSIVE DISORDER USING REWARD BEHAVIOR AND BRAIN FUNCTION*

Crystal Cooper*[1], *Adriane M. dela Cruz[1], Tracy L. Greer[1], Bailey Parsons[1], Engie Hamza[1], Cherise Chin Fatt[1], Maurizio Fava[2], Benji Kurian[1], Ramin Parsey[3], Patrick McGrath[4], Myrna Weissman[5], Diego Pizzagalli[2], Mary Phillips[6], Madhukar H. Trivedi[1]*

[1]The University of Texas Southwestern Medical Center, [2]Massachusetts General Hospital, [3]Stony Brook University, [4]New York State Psychiatric Institute, [5]Columbia University, [6]University of Pittsburgh School of Medicine

Abstract: Background: Major Depressive Disorder (MDD) is associated with blunted reward processing as assessed by behavior and brain function. These abnormalities are thought to be related to anhedonia, a cardinal symptom of MDD. Blunted reward processing in MDD can be contrasted against the high reward reactivity seen across patients with substances use disorders. The effect of a history of substance use disorder on reward processing in patients with MDD has not been characterized, and better understanding of these phenotypes will allow for the development of individualized treatments. We hypothesize reward processing to be different in those MDD participants that have a lifetime history of a substance use disorder (i.e., alcohol use disorder; MDD+AUD) versus those that do not (MDD-Only). In the present work, we sought to investigate reward processing (behavior and brain response) in a large sample of patients with early onset MDD, phenotyping by the presence of a history of an AUD.

Methods: Participants were 18-65 years old and participated in the multisite Establishing Moderators/Biosignatures of Antidepressant Response in Clinical care (EMBARC) study, a two phase, randomized, placebo-controlled trial of early onset MDD. Participants were age and gender matched providing 71 MDD+AUD participants and 134 MDD-Only participants. Prior to starting study medication, measures of anhedonia and reward behavior, using the Probabilistic reward task (PRT), were acquired. Participants were also scanned with an event-

related reward task (card guessing game). Analyses to compare the patient groups were performed on level of anhedonia, established measures of reward processing from the PRT, and reward response in key regions of the reward network (i.e., ventral striatum [VS] and anterior cingulate cortex [ACC]).
Results: The MDD+AUD group had greater anhedonia. Results show performance on the PRT task to be equivalent between MDD-Only and MDD+AUD. However, despite being able to learn from rewards like MDD-Only, MDD+AUD were slower to respond to items they have learned to be rewarded the most. During reward anticipation, the MDD+AUD group showed lower VS response than the MDD-Only group. During reward outcome, the MDD+AUD group showed deactivation of the ACC relative to the MDD-Only group.
Conclusion: Compared to MDD-Only, MDD+AUD participants had greater anhedonic symptoms and blunted reward responses in both behavior and brain markers of interest, a surprising result given that AUD was in remission at the time of assessment. These clinical, behavioral, and neural markers are important to differentiate when developing successful biomarkers of MDD. Future work is needed to investigate if these findings are the result of compensatory processes post-AUD or pre-existing conditions that put them at greater risk of developing an AUD.

Learning Objectives:

1. Characterize reward processing using behavior and brain function in those with Major Depressive Disorder (MDD) only and those with MDD and a history of a substance use disorder.
2. Demonstrate the need to understand differential reward processing within MDD as important for biomarker development in MDD.

Literature References:

1. Phillips ML, Chase HW, Sheline YI, Etkin A, Almeida JR, Deckersbach T, Trivedi MH. Identifying predictors, moderators, and mediators of antidepressant response in major depressive disorder: neuroimaging approaches. Am J Psychiatry 2015; 172:124-138.
2. Trivedi MH, McGrath PJ, Fava M, Parsey RV, Kurian BT, Phillips ML, Oquendo MA, Bruder G, Pizzagalli D, Toups M, Cooper CM, Adams P, Weyandt S, Morris DW, Grannemann BD, Ogden RT, Buckner R, McInnis M, Kraemer HC, Petkova E, Carmody TJ, Weissman MM. Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): Rationale and design. J Psychiatr Res 2016; 78:11-23.

Individual Research Reports: Exploring New Treatment Options in Diverse Populations* 4:15 p.m. - 5:30 p.m.

EFFICACY AND SAFETY OF LEMBOREXANT VERSUS PLACEBO IN ADULT AND ELDERLY SUBJECTS WITH INSOMNIA: 6-MONTH RESULTS FROM SUNRISE-2*

Jane Yardley[1], Kate Pinner[1], Gleb Filippov[1], Gary Zammit[2], Margaret Moline*[1]
[1]Eisai Inc., [2]Clinilabs Drug Development Corporation

Abstract: Introduction: Adult and elderly individuals commonly complain of difficulties with falling asleep and maintaining sleep throughout the night (Rodriguez, 2015). Many insomnia treatments are not indicated for sleep maintenance insomnia, the chief sleep complaint of elderly individuals, and the effectiveness of some treatments may decrease over time.

Lemborexant (LEM) is a dual orexin receptor antagonist in clinical development for insomnia (Murphy, 2017). Results from the 6-month, placebo (PBO)-controlled treatment period of a Phase 3 study of LEM are reported here.

Methods: SUNRISE-2 (NCT02952820) was a randomized, double-blind, PBO-controlled (first 6 months), 12-month, global Phase 3 study in adults aged ≥18y. Eligibility criteria included meeting DSM-5 criteria for insomnia disorder and current difficulties with sleep onset, sleep maintenance, or both, as confirmed by sleep diary. The study excluded subjects with other sleep disorders (e.g., moderate to severe sleep apnea, periodic limb movement disorder, restless legs syndrome, narcolepsy), but individuals with comorbid medical or psychiatric conditions that were sufficiently treated were allowed. Subjects were randomized to PBO or LEM (5mg, [LEM5] or 10mg, [LEM10]) for 6 months, following an ~2-week single-blind PBO Run-in Period. At the 6-month visit, subjects from the PBO treatment group were re-randomized to LEM5 or LEM10 (to be reported elsewhere). Study drug was taken within 5 min of bedtime. Subjects completed a sleep diary each morning of the study. Efficacy assessments included subjective sleep onset latency (sSOL), subjective wake after sleep onset (sWASO), and subjective sleep efficiency (sSE); SE was defined as total sleep time divided by time in bed.

Results: The full analysis set comprised 949 randomized subjects (PBO, n=318; LEM5, n=316; LEM10, n=315). The median age was 55y, and 262 (27.6%) subjects were aged ≥65y. The majority of subjects (>70%) completed the first 6 months of treatment.

After 6 months, both LEM5 and LEM10 significantly shortened median sSOL change from baseline (min) vs PBO (LEM5: −21.8; LEM10: −28.2 vs PBO: −11.4; P<0.0001 both doses). Also, the least squares mean (LSM) increase from baseline in sSE (%) was significantly larger vs PBO in both groups (LEM5: 14.2; LEM10: 14.3; vs PBO: 9.6; P≤0.0001 both doses) and both LEM5 and LEM10 significantly reduced sWASO (min) more than PBO (LSM change from baseline: PBO, −29.3; LEM5, −46.8 [P=0.0005 vs PBO]; LEM10, −41.9 [P=0.0105 vs PBO]). For all 3 parameters, the larger differences from baseline vs PBO were also statistically significant during the first week of treatment (P<0.0001 for both doses).

Most adverse events (AEs) were mild or moderate in severity. Serious AEs occurred in 1.6% of the PBO group, 2.2% of the LEM5 group, and 2.9% of the LEM10 group. The most common AEs (occurring in >5% of subjects in any active treatment group and >PBO) were somnolence (1.6% [PBO]; 8.6% [LEM5]; and 13.1% [LEM10]); headache (6.6% [PBO]; 8.9% [LEM5]; 6.7% [LEM10]); and influenza (4.7% [PBO]; 4.8% [LEM5]; 5.1% [LEM10]).

Conclusions: Treatment with LEM led to larger differences from baseline in both sleep onset and sleep maintenance parameters vs PBO at the beginning (first 7 nights) and end of 6 months of treatment. LEM was well tolerated. Results from SUNRISE-2 support the growing evidence for LEM as a potential treatment for insomnia disorder.

Support: Eisai Inc. and Purdue

Learning Objectives:

1. To describe the long-term safety of lemborexant in subjects with insomnia disorder.
2. To describe the long-term efficacy of lemborexant in subjects with insomnia disorder.

Literature References:

1. Rodriguez JC, Dzierzewski JM, Alessi CA: Sleep problems in the elderly. Med Clin North Am 2015; 99:431-9.
2. Murphy P, Moline M, Mayleben D, et al: Lemborexant, A Dual Orexin Receptor Antagonist (DORA) for the Treatment of Insomnia Disorder: Results From a Bayesian, Adaptive, Randomized, Double-Blind, Placebo-Controlled Study. J Clin Sleep Med 2017; 13(11):1289-99.

SERIOUS MENTAL ILLNESS AMONG NEWLY ADMITTED WORKING-AGE NURSING HOME RESIDENTS*

Christine Ulbricht*[1], *Yiyang Yuan*[1], *Hye Sung Min*[1], *Kate Lapane*[1]
[1]*University of Massachusetts Medical School*

Abstract: Introduction: Nursing homes in the U.S. serve more adults with mental illness than all other healthcare facilities combined. Nursing home care may be inappropriately substituted for community-based care and specialty psychiatric long-term care, particularly for those with serious mental illness (SMI). Understanding the extent to which working-age adults with SMI reside in these facilities and their complex health care needs is important for improving processes of care for this neglected population. The study objectives were to: 1) describe the sociodemographic and clinical characteristics of working-age adults with SMI newly admitted to nursing homes; and 2) describe the psychopharmacological treatment received by these residents.
Methods: Data from the 2014 national Minimum Data Set (MDS) 3.0 were used to identify 62,079 working age adults (aged 18 to 64 years) with SMI who were newly admitted to U.S. nursing homes. A broad definition of SMI was used: schizophrenia, other psychotic disorder, bipolar disorder, depression, and/or an anxiety disorder. MDS 3.0 is federally-mandated and as such is completed for all residents of all Medicare-/Medicaid-certified nursing facilities. The MDS 3.0 is a comprehensive assessment that includes validated measures of active clinical diagnoses, physical functioning, and pharmacological and non-pharmacological treatments. Receipt of psychotropic medication included antidepressants, antianxiety medication, antipsychotics, and hypnotics received at any time in the seven days before the assessment.
Results: Almost one sixth (15.0%, n = 12,693) of working-age nursing home residents with SMI were 18-49 years old. Men comprised nearly half (46.0%) of all working-age residents with SMI. The majority (95.1%) of the working-age residents with SMI required assistance with activities of daily living. Slightly more than one third (36.4%) had at least three physical comorbidities. The most commonly documented active psychiatric diagnosis among them was depression (72.3%), followed by an anxiety disorder (45.9%) and schizophrenia (13.7%). Approximately 23% had both depression and an anxiety disorder. Almost all (92.3%) received at least one type of psychotropic medication, with 47.5% receiving two or more different types. Antidepressants were the most common type of psychotropic medication received (72.4% of residents). Antianxiety and antipsychotic medications were each received by about a third (antianxiety medications = 39.1%; antipsychotics = 32.0%).
Conclusions: Working-age adults with SMI reside in nursing homes and likely have complex care needs. Additional research on treatment need and trajectories of functioning throughout the nursing home stay is necessary for understanding the quality of life for these adults and their likelihood of returning to the community.

Learning Objectives:

1. To recognize the prevalence and correlates of serious mental illness among working-age nursing home residents.
2. To understand important issues in providing mental health treatment to working-age nursing home residents with serious mental illness.

Literature References:

1. Fullerton CA, McGuire TG, Feng Z, et al: Trends in mental health admissions to nursing homes, 1999-2005. Psychiatr Serv 2009; 60(7):965-971
2. Grabowski DC, Aschbrenner KA, Rome VF, et al: Quality of mental health care for nursing home residents: a literature review. Med Care Res Rev 2010; 67(6):627-656

PHARMACOGENOMIC STUDY OF ANTIPSYCHOTIC MEDICINES IN CHINESE HAN POPULATION*

Hao Yu[1], Lifang Wang[2], Jun Li[2], Tianlan Lu[2], Liwen Tan[3], Wei Deng[4], Qi Chen[5], Guigang Yang[6], Lili Guan**[2]
[1]Jining Medical University, [2]Peking University Sixth Hospital, [3]Central South University Institute of Mental Health, [4]Sichuan University Mental Health Center, [5]Capital Medical University Beijing Anding Hospital, [6]Beijing Huilongguan Hospital
Lili Guan, Peking University

Abstract: In the present study, we did a two-stage pharmacogenomic genome-wide association study of treatment response or antipsychotic-induced weight gain (AIWG) in patients with schizophrenia. The patients randomly assigned to aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, haloperidol, and perphenazine. The sample size of this study (n=2413 in the discovery cohort and 1379 in the replication samples) is one of the largest reported so far.

We have detected five novel significant loci (MEGF10, SLC1A1, PCDH7, CNTNAP5, and TNIK) associated with general treatment response (i.e., combining all antipsychotics). We calculated the genetic risk score on the basis of five significant SNPs, the discriminative power to distinguish responders from non-responders remained moderate (best area under the curve 71.3%).

For the AIWG, the two-stage GWAS identified two genome-wide significant SNPs with AIWG at two genes: the PTPRD gene (protein tyrosine phosphatase, receptor type D; rs10978083, P=4.34×10-12) and PEPD gene (peptidase D; rs731839, P=5.50×10-10), respectively. Furthermore, the polygenic risk score calculated based on the two SNPs (rs10978083 and rs731839) could significantly predict AIWG in the discovery (P=1.47×10-12) and follow-up cohort (P=1.39×10–2).

We have identified genes related to synaptic function, neurotransmitter receptors, and schizophrenia risk that are associated with response to antipsychotics. We have also identified genes related to metabolic process that are associated with AIWG. These findings improve understanding of the mechanisms underlying treatment responses, and the identified biomarkers could eventually guide choice of antipsychotic in patients with schizophrenia.

Learning Objectives:

1. Pharmacogenomic study
2. Antipsychotic medicines

Literature References:

1. Yu H, Yan H, Wang L, Li J, Tan L, Deng W, Chen Q, Yang G, Zhang F, Lu T, Yang J, Li K, Lv L, Tan Q, Zhang H, Xiao X, Li M, Ma X, Yang F, Li L, Wang C, Li T, Zhang D, Yue W*, Chinese Antipsychotics Pharmacogenomics Consortium. Five novel loci associated with antipsychotic treatment response in patients with schizophrenia: a genome-wide association study. Lancet Psychiatry 2018;5(4):327-338.
2. Yu H, Wang L, Lv L, Ma C, Du B, Lu T, Jin C, Yan H, Yang Y, Li W, Ruan Y, Zhang H, Zhang H, Mi W, Mowry B, Ma W, Li K, Zhang D, Yue W*. Genome-wide association study suggested the PTPRD polymorphisms were associated with weight gain effects of atypical antipsychotic medications. Schizophr Bull 2016; 42(3): 814-23.

GENETIC DIFFERENTIAL DIAGNOSIS IN HIGHLY TREATMENT RESISTANT SCHIZOPHRENIA*

Martilias Farrell*[1], *Maya Lichtenstein*[2], *James Crowley*[1], *Dawn Filmyer*[3], *Gabriel Lázaro-Muñoz*[4], *Rita Shaughnessy*[3], *Tyler Dietterich*[3], *Matthew Halvorsen*[1], *Lisa Bruno*[3], *Matt Harner*[3], *James Evans*[1], *Jonathan Berg*[1], *Jin Szatkiewicz*[1], *Richard Josiassen*[5], *Patrick Sullivan*[6]

[1]*University of North Carolina at Chapel Hill,* [2]*Geisinger Health System,* [3]*Translational Neuroscience, LLC,* [4]*Center for Medical Ethics and Health Policy, Baylor College of Medicine,* [5]*Translation Neuroscience, LLC, Drexel University College of Medicine,* [6]*University of North Carolina at Chapel Hill; Karolinska Institutet*

Abstract: Purpose: Schizophrenia (SCZ) is an idiopathic mental disorder with substantial morbidity, mortality, and personal-societal costs. Understanding its molecular basis is one of the most significant problems in psychiatry, as this could lead to better and targeted therapeutics. The primary medical intervention for schizophrenia is the use of antipsychotic drugs (APDs). Most individuals with SCZ respond to APDs, though a large percentage of people do not respond to these medications. We hypothesize that people with highly treatment resistant schizophrenia (HTRS) may actually have undiagnosed rare genetic disorders that present as schizophrenia. If these disorders can be identified, these differential diagnoses may lead to a more efficacious medical intervention. The purpose of our research is to characterize the genetic architecture of HTRS and simultaneously explore the utility of genomic screening as a differential diagnostic tool for psychiatry.

Methods: An ideal HTRS subject is actively treated with a tailored therapeutic regimen, is adherent to prescribed medications, resides in a protected environment, is protected from illicit drug use, and yet has been severely psychotic for years. The Pennsylvania (PA) state psychiatric hospitals contain an ideal HTRS sample. To test this hypothesis, we screened individuals with HTRS for genetic variation that may explain their highly treatment resistant status. We have recruited, assessed and assayed n=491 participants from the PA State Hospital system. Our formal inclusion criteria are: provision of written informed consent; age ≥18 years (either sex and any ancestry); DSM-IV diagnosis of SCZ, schizoaffective disorder, or psychosis NOS; ≥5 years of continuous inpatient hospitalization in one of the PA state hospitals; ≥5 years of persistent psychotic symptoms with GAF scores ≤40 over the course of documented hospitalization; a history of poor treatment response to adequate trials of ≥3 different classes of antipsychotic drugs at recommended maximum dose in trials lasting ≥6 weeks. Medications must include a first-generation antipsychotic and two second-generation antipsychotics (e.g., HTRS with adequate trials of haloperidol, clozapine, and quetiapine). Our exclusion criteria are as follows: DSM-IV psychotic disorder consequent to licit or illicit drug dependence; sustained treatment response (GAF score >40 for any 3-month period); or sustained refusal to take prescribed medications (>5% of the 5-year screening window). DNA from these individuals was assayed using the Global Screening Array (GSA) and Whole Exome Sequencing (WES). CNVs were called using PennCNV, SNVs were called using GATK, and VNTRs were called using ExpansionHunter.

Results: Our preliminary screening indicates that 35 individuals have a CNV over 750kb, 316 individuals have a CNV over 100kb, and 53 individuals have CNVs that overlap with CNVs that have been previously associated with schizophrenia. 85 individuals carry a ClinVar pathogenic variant in a gene associated with a Mendelian disorder that presents as SCZ.

Importance: Our preliminary findings suggest that our sample may contain a novel source of genotype-phenotype relationships that can be used to identify clinically useful variation for etiological research, clinical utility, and therapeutic development. We propose that our findings are important because they demonstrate the utility of genetics in psychiatry for differential diagnoses that may guide the clinical course towards more efficacious medical interventions.

Learning Objectives:

1. The participant will learn that genomic technology has clinical utility in a severe subset of schizophrenia patients.
2. The participant will gain an overview of psychiatric genomics.

Literature References:

1. Farrell M, Lichtenstein M, Crowley JJ, Filmyer DM, Lazaro-Munoz G, Shaughnessy RA, et al. Developmental Delay, Treatment-Resistant Psychosis, and Early-Onset Dementia in a Man With 22q11 Deletion Syndrome and Huntington's Disease. Am J Psychiatry. 2018;175(5):400-7.
2. Lázaro-Muñoz G, Farrell MS, Crowley JJ, Filmyer DM, Shaughnessy RA, Josiassen RC, et al. Improved ethical guidance for the return of results from psychiatric genomics research. Molecular Psychiatry. 2017.

Individual Research Reports: Using MDMA and Transdermal Buprenorphine to Treat Trauma and Addiction, Microbiome Changes in Binge Drinking, and Understanding Why Our Phase III Trials can Fail Even When the Treatment Works*
4:15 p.m. - 5:30 p.m.

A PROPOSED UTILITY OF WEEKLY BUPRENORPHINE TRANSDERMAL PATCH (BUP-TD) AS A VIABLE OPTION FOR DETOXIFICATION OR MAINTENANCE THERAPY FOR OPIOID USE DISORDER*

Rahim Shafa[1], Mona Ghavami[2], George Ide*[3]
[1]NCPE Novel Clinical Psychopharmacology Care, [2]Icahn School of Medicine at Mount Sinai, [3]NYCHHC

Abstract: Background: Initiation of agonist therapy for OUD with Sublingual Buprenorphine requires a period of opiate abstinence, 24 hours off of short acting opiates and up to 96 hours off of Methadone, before the process of "Induction" can be safely tolerated. Buprenorphine has strong Mu receptor affinity which also creates an advantageous deterrent to illicit use of opiates but also displaces a opiates/opioids such as morphine. This property enables buprenorphine to effectively act as a dual agent while treating opiate withdrawal symptoms. A previous phase 1 study conducted in 2007, involving nine inpatient opioid-dependent subjects, resulted in BUP-TD demonstrating safety and tolerability while providing adequate suppression of opioid withdrawal syndrome (Lanier Et al).

In this study, we utilized the weekly Buprenorphine transdermal patch, approved by the FDA for chronic pain management, as a treatment method to detoxify an opioid dependent population, in an outpatient setting, facing the obstacle of withdrawal hindering the initiation of buprenorphine treatment. BUP-TD was used as a method to overcome the obstacle of oral induction in a patient population unable to abstain long enough to tolerate the induction phase. Upon administration of a single dose BUP-TD, the pharmacokinetic properties allowed the buprenorphine blood levels to progressively increase towards the maximum level by day 3, plateau through day 7, and then taper to a negligible level by day 14 (Andresen Et al). According to FDA guidelines, concomitant administration of opioids in the first 3 days of BUP-TD treatment will not cause a withdrawal reaction. Therefore, utilizing BUP-TD eliminates the need for initial opiate withdrawal to induce Buprenorphine treatment. But more importantly, the inherent automated gradual titrate-taper delivery property of BUP-TD allows for it to be a candidate for an opioid detox protocol.

Methods: The study was conducted at an outpatient chemical dependency treatment center in Boston, Massachusetts, between 2009 and 2016. Fifty-five (55) recalcitrant opiate dependent

adults provided informed consent to participate in the open-label study of the utilization of BUP-TD to transition to buprenorphine treatment or be completely detoxed from opioids (patient choice) and be given Naltrexone Maintenance therapy. Each subject was initiated with 5 Mcg/h patch (BUP-TD), with the dose titrated to the optimum level. Patients who chose to be completely detoxified, were kept on the same strength transdermal patch for up to 12 days. In addition, subjects were given clonidine (as needed) for the first 72 hours of the induction phase. Clonidine was also given to the detoxifying population between days 7-14, to assist with the detox protocol. Each subject was closely monitored with three weekly visits. Study outcome was measured by frequent patient interviews and LCMS/GCMS toxicology screens. The detoxing population was challenged with two doses of 50 mg oral Naltrexone on days 14 and 15 and after which they began long-acting naltrexone.

Results: Ninety-four percent (94%) of subjects reached the primary goal, reaching BUP-TD initiation, while 60% of subjects achieved abstinence. Thirteen percent (13%) of subjects who tolerated induction, chose to continue on oral Buprenorphine, with 42% relapsing during the protocol.

Conclusion: BUP-TD may have a utility in opiate detox among a recalcitrant population. BUP-TD may assist those who are unable to initiate oral Buprenorphine treatment and play an effective role in a personalized detoxification plan. The transdermal formulation may also help overcome compliance concerns and deliver buprenorphine in a formulation likely to be diverted for diversion/illicit use.

Learning Objectives:

1. Better understanding and approach in developing a personalized strategy for opioid detoxification in difficult patient populations.
2. Understand the pharmacokinetics of alternative methods for buprenorphine induction in difficult patient populations and share our success with transdermal buprenorphine to inspire future studies.

Literature References:

1. Andresen, T., Upton, R. N., Foster, D. J., Christrup, L. L., Arendt-Nielsen, L., & Drewes, A. M. (2010). Pharmacokinetic/Pharmacodynamic Relationships of Transdermal Buprenorphine and Fentanyl in Experimental Human Pain Models. Basic & Clinical Pharmacology & Toxicology, 108(4), 274-284. doi:10.1111/j.1742-7843.2010.00649.x
2. Lanier, R. K., Umbricht, A., Harrison, J. A., Nuwayser, E. S., & Bigelow, G. E. (2007). Evaluation of a transdermal buprenorphine formulation in opioid detoxification. Addiction, 102(10), 1648-1656. doi:10.1111/j.1360-0443.2007.01944.x

ANALYSIS OF THE GUT MICROBIOME IN A BABOON MODEL OF ALCOHOL BINGE DRINKING*

Daria Piacentino*[1], *Silvia Beurmann[2], Mary Lee[3], Samantha Womack[4], Claire Fraser[5], Elise Weerts[6], Lorenzo Leggio[3]*

[1]NIH/NIAAA, [2]Institute for Genome Sciences, University of Maryland, [3]National Institute on Alcohol Abuse and Alcoholism and Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Center for Alcohol and Addiction Studies, Brown University, [4]Duke University, [5]Institute for Genome Sciences, University of Maryland School of Medicine, [6]Johns Hopkins University

Abstract: Introduction: Consistent with the key interplay between the gut and the central nervous system, the gut microbiome is gaining attention as a potential modulator of psychological processes and mental health disorders. About 1014 bacteria constitute the

community residing in the gut, predominated by the phyla Firmicutes and Bacteroidetes. The overall balance of this community determines the gut homeostasis. Diet and dietary energy intake may impact the composition of the gut microbiome (Fontana & Partridge, 2015). Alcohol, in addition of being a drug, is a source of calories and may thus affect the gut microbiome. Very little is known on the role of the gut microbiome in alcohol use disorder (AUD) and whether the microbiome-gut-brain axis may be involved in the mechanisms that regulate alcohol binge drinking (Temko et al., 2017).

Aims: To provide the first descriptive analysis of the gut microbiome in a unique non-human primate model of alcohol binge drinking. The long-term goal is to understand if binge drinking is associated with significant traits of the gut microbiome and if manipulations of the gut microbiome may lead to changes in alcohol-seeking behaviors.

Materials & Methods: We analyzed the gut microbiome on fecal samples from male baboons chronically exposed to either alcohol or a non-alcoholic isocaloric beverage (tang). Specifically, there were three treatment groups: G1 = tang (control); G2 = "short-term" alcohol binge drink group (2-3 yrs); and G3 = "long-term" alcohol binge drink group (~10 yrs). Diet was similar for all groups (standard primate biscuits plus 1 piece of fruit supplement). Fecal samples were collected in one of two conditions: A = early abstinence (days 3-5) and B = during 3 days of ongoing drinking. All fecal samples were placed in RNAlater and frozen at -80 °C for further analyses. To determine microbiome changes, the relative abundances were compared using Linear Discriminant Analysis Effect Size (LEfSe).

Results: Microbial α-diversity (Shannon Diversity Index) was significantly lower in the G3 group vs. the G1/G2 groups. LEfSe detected several clades showing statistically significant and biologically consistent differences among the three cohorts. The two genera Lactobacillus and Streptococcus showed overall higher relative abundances in G3. Faecalibacterium was reduced in G3 only. For G2, the order Clostridiales and the family Ruminococcaceae showed high relative abundances compared to G1 and G3. Cohort G1 showed members of the family Anaeroplasmataceae to be more abundant. No significant difference was found between Conditions A and B.

Conclusions: Our findings suggest that in alcohol binge drinking baboons, compared to the control cohort, long-term protracted exposure to alcohol binge drinking (G3) leads to significant changes in the gut microbiome, whereas relatively short-term alcohol exposure (G2) does not significantly alter it. These changes are not affected by acute forced withdrawal from chronic alcohol exposure, as we found no difference between Conditions A and B. Our results are novel, given that they were generated from a unique non-human primate model of alcohol binge drinking, whose microbiome has not been studied before. Ongoing projects are baboon stool metabolome analysis and preliminary translational bed-to-bench work through human stool collection aimed at investigating gut microbiome differences in current drinking vs. abstinent individuals with AUD and the potential correlation with alcohol cue-induced craving.

Learning Objectives:

1. Be informed of the emerging research endeavors in the field of psychopharmacology and be mentored by experts in the field in order to improve the quality of my study.
2. Build productive collaborations with members of NIH, FDA, academia, and pharmaceutical industry, which will help me gain new insights in clinical and translational research in the addiction field.

Literature References:

1. Fontana, L, Partridge, L. (2015). Promoting health and longevity through diet: from model organisms to humans. Cell, 161(1), 106-118.
2. Temko, J.E, Bouhlal, S, Farokhnia, M, Lee, M.R, Cryan, J.F, Leggio, L. (2017). The microbiota, the gut and the brain in eating and alcohol use disorders: A 'ménage à trois'? Alcohol and Alcoholism, 52(4), 403-413.

GIVE US YOUR TIRED, YOUR POOR, YOUR PROFESSIONAL SUBJECTS: THE LAST QUARTILE OF PHASE 3 ENROLLMENT

Thomas Shiovitz*[1], *Brittany Steinmiller*[2], *Chelsea Steinmetz*[2], *Faye Golden*[2]
[1]*California Neuroscience Research,* [2]*CTSdatabase, LLC*

Abstract: Background and Purpose: Duplicate and Professional subjects affect safety and efficacy signals in clinical trials. These subjects may magnify inclusion criteria or be deceptive about exclusion criteria and often change their presentation (or their diagnosis) as they go from site to site collecting stipends. This is particularly well-described clinical trials in CNS and in pain, where subjective endpoints facilitate the deception. In Phase 2-4 studies, professional subjects often do not take study medication, even as they report perfect or near-perfect adherence. Identifying and eliminating these subjects through use of a subject registry may be one simple and cost-effective mitigation strategy to prevent the contamination of the ITT (Intent-To-Treat) sample with these inappropriate subjects.
Methods and Results: CTSdatabase is a subject registry of over 50,000 Ph 2-4 clinical trial subjects, predominantly in CNS and pain. We looked at adult Phase 2 and 3 subjects(n=6997) from 7 completed studies in Schizophrenia, Major Depressive Disorder (MDD), Binge-Eating Disorder (BED), Attention Deficit Hyperactivity Disorder (ADHD) and Fibromyalgia where the registry was used from start to finish. For each study we divided the subjects by quartile of enrollment, looked at the number of subjects who were excluded for being duplicate enrollers or for otherwise violating I/E criteria, such as participating in another study too recently or for an exclusionary indication (such as schizophrenia for an MDD study). We then pooled the results and looked for significance by phase of study and by quartile of enrollment. When Phase 2 and early (Q1 and Q2) Phase 3 subjects were compared to late Phase 3 (Q3+Q4) subjects, there was a highly significant increase ($p<.001$) in the number and percentage of inappropriate subjects identified by the registry in the second half of Phase 3 enrollment.
Importance: This data suggests that the subjects entered into the latter part of Phase 3 studies are different, i.e. more likely inappropriate/duplicate/professional, than in Phase 2 and Early Phase 3 studies. If this data is confirmed, and subjects in late Phase 3 studies are significantly different from those in Phase 2 studies, this might partially explain why successful Phase 2 studies frequently lead to failed Phase 3 studies. Further efforts could be then be taken (e.g. through study design and sample size calculation, use of subject registries, pharmacokinetic sampling and adherence technologies) to mitigate the increased effects of inappropriate subjects on Phase 3 study outcomes.

Learning Objectives:

1. Participants will be able to list at least two ways that professional subjects can adversely affect safety and efficacy signals in clinical trials (Answers: a. by not taking IP leading to a loss of study power, b. by taking IP in more than one study at the same time affecting patient safety, c. by magnifying inclusion ratings at study entry, d. by not mentioning concurrent conditions at study entry).
2. Participants will be able to describe at least 2 ways that the problem of inappropriate subjects might be mitigated in Phase 3 clinical trials (Answers: a. using Ph 2 data in Phase 2 to inform Ph 3 study design, b. use of a subject registry and or adherence technology, c. use of PK data or ratings algorithms).

Literature References:

1. Shiovitz TM, Bain EE, McCann DJ, et al: Mitigating the Effects of Nonadherence in Clinical Trials. J Clin Pharmacol 2016; 56(9): 1151-1164.
2. McCann D, Petry NM, Bresell AI, et al: Medication nonadherence, "professional subjects", and apparent placebo responders: overlapping challenges for medications development. J Clin Psychopharmacol 2015; 35(1): 566-573.
3. Lee CP, Holmes T, Neri E, et al: Deception in clinical trials and its impact on recruitment and adherence of study participants. Contemp Clin Trials 2018; 72: 146-157.

AN OPEN-LABEL, MULTI-SITE PHASE 2 MDMA-ASSISTED PSYCHOTHERAPY TRIAL FOR SEVERE POSTTRAUMATIC STRESS DISORDER AND SUPERVISION OF NEW CO-THERAPY TEAMS*

Allison Feduccia*[1], *Lisa Jerome*[1], *Berra Yazar-Klosinski*[2], *Amy Emerson*[1], *Michael Mithoefer*[3]
[1]*MAPS Public Benefit Corporation,* [2]*Multidisciplinary Assn. for Psychedelic Studies,* [3]*Medical University of South Carolina*

Abstract: Background: The Multidisciplinary Association for Psychedelic Studies (MAPS) completed six FDA-regulated Phase 2 clinical trials of MDMA-assisted psychotherapy for the treatment of posttraumatic stress disorder (PTSD). The FDA granted Breakthrough Therapy designation for this novel approach and agreed to plans for Phase 3 trials in USA, Canada, and Israel. New therapy teams were trained for 15 phase 3 study sites. As the final step in the multi-part MAPS Therapy Training Program, new therapy teams treated one open-label participant in a phase 2 trial (MP-16) with an identical study design as phase 3 and received clinical supervision from the training team.

Methods: An open-label phase 2 trial investigated a flexible dosing regimen of MDMA (80-120 mg) during 3 psychotherapy sessions that were each followed by 3 non-drug integrative sessions. The 12-week treatment period was preceded by three preparatory sessions. Participants with severe PTSD and a Clinician Administered PTSD scale (CAPS-5) Total Score of 35 were enrolled (max n=60) after meeting all other inclusion/exclusion criteria. An independent rater pool administered the CAPS-5. Safety measures were collected throughout the study. The primary endpoint was two months after the third MDMA session (data collection underway until spring 2019).

Results: At the primary endpoint, CAPS-5 total scores had significantly declined compared to baseline ($p < 0.001$, n=25) with a mean (SD) decrease of -31.9 (12.07). According to the CAPS, 84% did not meet PTSD criteria at the primary endpoint. Physiological vital signs and adverse event rates support an acceptable risk/benefit ratio. All new therapy teams passed the supervision phase of the training program by demonstrating competency in delivering this manualized treatment approach.

Conclusion: MDMA treatment was well-tolerated in these controlled clinical settings and led to robust reductions in PTSD symptom severity. All therapy teams passed the supervision period and were well prepared for the first phase 3 trial that started in November 2018. If findings are replicated in two phase 3, MDMA-assisted psychotherapy for treatment of PTSD could be FDA-approved by 2021.

Learning Objectives:

1. Understand the rationale, study designs, and drug development program for MDMA-assisted psychotherapy for treatment of PTSD.
2. Describe the safety and efficacy outcomes of MDMA-assisted psychotherapy phase 2 trials, and the therapeutic approach employed for use of MDMA in therapy.

Literature References:

1. Feduccia, AA, Holland, J, & Mithoefer, MC: Progress and promise for the MDMA drug development program. Psychopharmacology 2018; 1-11.
2. Mithoefer, MC, Mithoefer, AT, Feduccia, AA, et al: 3, 4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. The Lancet Psychiatry 201; 5(6): 486-497.

Wednesday, May 29, 2019

Regulatory Plenary
8:30 a.m. - 10:00 a.m.

REGULATORY PLENARY: BREAKTHROUGH AND PRIME REGULATORY PATHWAYS

William Potter, National Institute of Mental Health

Overall Abstract: This year's Regulatory Plenary will focus on FDA and EMA initiatives intended to help address unmet medical needs. FDA will discuss the Breakthrough Therapy Designation program and highlight recent approvals of Breakthrough-designated products with psychiatric indications. EMA will provide a similar update, focusing on the PRIority MEdicines (PRIME) scheme, as well as a comparison of the two programs and their benefits.

US AND EUROPEAN REGULATORY PROGRAMS TO FACILITATE DRUG DEVELOPMENT FOR SERIOUS CONDITIONS

Tiffany Farchione, US Food and Drug Administration

Abstract: Regulatory Agencies have a several pathways at their disposal to facilitate drug development of drug products that treat serious conditions or fulfill unmet medical needs.
During this session, these processes will be reviewed and compared in terms of assessment, incentives, timelines and outcome.
FDA will review its Breakthrough Therapy program with a focus on recent approvals of Breakthrough-designated products. FDA will describe ways in which the Breakthrough Therapy program facilitated the development, review, and ultimate approval of valbenazine, esketamine, and brexanolone.

Learning Objectives:

1. Developers will learn how to interact with programs in support of innovation and unmet needs.
2. Researchers will learn available incentives to support clinical research carried out by academia and pathways in support of regulatory knowledge for academic groups.

Literature References:

1. Food and Drug Administration. (2014) Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics
2. https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf
3. Mullard A. PRIME time at the EMA. Nat Rev Drug Discov. 2017 Mar 30;16(4):226-228. doi: 10.1038/nrd.2017.57

COMPARING BREAKTHROUGH THERAPY AND PRIME, INCLUDING ASSESSMENT, TIMELINES, BENEFITS, OUTCOMES, AND REGULATORY PATHWAYS

Valentina Mantua, Italian Medicines Agency

Abstract: EMA will present general descriptive data on the first two years of the PRIME scheme. EMA will map regulatory pathways connecting PRIME with other EU initiatives in support of innovative products such as the EU-Innovation Network. EMA will also provide an overview of the CNS products that were granted eligibility for PRIME.

Learning Objectives:

1. Developers will learn how to interact with programs in support of innovation and unmet needs at an EU level.
2. Researchers will learn available incentives to support clinical research carried out by academia and pathways in support of regulatory knowledge for academic groups.

Literature References:

1. Mullard A. PRIME time at the EMA. Nat Rev Drug Discov. 2017 Mar 30;16(4):226-228. doi: 10.1038/nrd.2017.57.

ASCP Awards Ceremony and ASCP Lifetime Awardee Talk
10:15 a.m. - 11:15 a.m.

FORTY YEARS OF RESEARCH AND PRACTICE IN PSYCHOPHARMACOLOGY

Alan Schatzberg, Stanford Univ. School of Medicine

Abstract: Psychopharmacology has evolved greatly in the last 4 decades. We have had the introduction of a variety of effective agents for treating patients with depression, bipolar disorder, schizophrenia, etc. This presentation will review the experience of the Awardee in the field over these last 40 plus years. The presentation will emphasize the pluses and minuses of antidepressant drug development, including: discussion of research into side effects of the first generation agents, relative efficacy of second generation agents in more severely ill patients, need for novel treatments with unique mechanisms of action for severe and psychotic major depressions; risk of developing potential drugs of abuse for the treatment of refractory depression, and the application of biomarkers for guiding treatment decisions.

Learning Objectives:

1. To discuss the risk/benefit of potential drugs of abuse as antidepressants.

Literature References:

1. Schatzberg AF, DeBattista C: Schatzberg's Manual of Clinical Psychopharmacology, 9th Edition. Washington, DC, American Psychiatric Publishing, 2019

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

BAD BEHAVIOR IN CLINICAL TRIALS: STRATEGIES TO COMBAT RESEARCH PARTICIPANT DISHONESTY/DECEPTION, NON-ADHERENCE, AND "PROFESSIONAL SUBJECTS"

Daniel Falk, NIAAA/NIH

Overall Abstract: The goal of this panel is to provide 3 presentations on topics related to research participant dishonesty/deception in pharmacotherapy clinical trials. It has become common practice to financially compensate research subjects for their time and inconvenience when participating in clinical studies; unfortunately, this practice creates and attracts "professional subjects," defined herein as subjects who participate in clinical research ONLY for financial gain. A worrisome example in the alcohol field would be an unemployed, alcohol-dependent subject who enrolls in a medication efficacy trial (for the treatment of AUD) simply to earn "beer money," and with no intention of taking study medication or trying to quit or reduce drinking. Because successful deception goes undetected, the full extent of the problem is unknown. However, its potential impact on clinical research cannot be ignored. Subjects expose themselves to increased risk when they withhold information from study investigators (for example, when they surreptitiously participate in simultaneous studies). In addition, the practice of deception threatens study integrity; efficacy outcomes for professional subjects who participate in medication trials may mask "real-word efficacy" that would be apparent in treatment-seeking patients.

Eric Devine will discuss the risks of enrolling professional subjects in clinical research and present data on the lifetime base-rates of subjects using deceptive behavior to gain entry into clinical trials. He will also discuss practical strategies researchers can use to exclude subjects who conceal and fabricate information when enrolling in clinical trials. Kerri Weingard will present rates of subjects who intentionally violate clinical trial inclusion/exclusion criteria protocols, including traveling to different sites within a study (14%) and health condition crossover (16%). She will further discuss how a global research subject database registry prospectively assessed and prevented these protocol violations in clinical trials. Amanda Paley will of describe how computerized artificial intelligence systems can be used to identify fraudulent non-adherence to medication protocol in clinical research, i.e., participants who intentionally cheat and not take study medication. She will present data on when this typically occurs (first 2 weeks of a trial), describe the impact on data quality and trial outcomes, and present trial enrichment strategies that may be used to remove fraudulent subjects before they are randomized.

This panel will alert clinical pharmacotherapy researchers to deceptive behavior of professional subjects and how this can detrimentally impact the integrity of the research. Practical and effective strategies will be discussed for combatting these deceptive subjects.

Learning Objectives:

1. To understand the detrimental effects to research integrity of subjects who use deception to gain entry into pharmacotherapy trials.
2. To become familiar with practical and effective strategies to prevent subject deception.

RATES OF SUBJECT DECEPTION IN CLINICAL RESEARCH AND PRACTICAL STRATEGIES TO MINIMIZE THE RISK OF ENROLLING PROFESSIONAL SUBJECTS IN CLINICAL RESEARCH

Eric Devine, Boston University School of Medicine

Individual Abstract: One of the greatest challenges in clinical research today is recruiting sufficient numbers of qualified subjects. Subjects who enroll in multiple trials for the purpose of generating income ("professional subjects") may be readily available but present a potential threat to study integrity due to the practice of lying in order to qualify for clinical trials. There is mounting evidence that study participants conceal recreational drug use, conceal nicotine use, lie when answering screening questions, enroll in the same study more than once, share strategies for evading the restrictive entry criteria of studies, and enroll in multiple studies simultaneously. Although the full extent of subjects using deception in clinical research is largely unknown and challenging to estimate, statistical models of the impact of even a small percentage of professional subjects lying to gain entry reveals the possibility that many studies may be underpowered for the primary outcome if professional subjects are enrolled. It is important for clinical researchers to understand the variety of deceptive strategies that professional subjects use in order to better implement safeguards against deception within the design of studies. In this panel discussion, I will present the results of a survey of "experienced" research subjects that was designed to detect the lifetimes base rates of using deceptive practices to screen and enroll in clinical trials. These findings will highlight deceptive practices including concealing health data, fabricating health conditions to qualify for a study, doing self-harm to qualify for a study, and using strategies to "hack" study screening processes. These findings will also include data regarding the health information that is most often concealed during screening. In this panel, I will also discuss a range of practical strategies for developing and implementing a study protocol with protections to minimize the enrollment of profession subjects. This discussion will include recommendations for advertising strategies, payment strategies, telephone screening strategies, and baseline screening strategies. I will also discuss recommendations for attending to inconsistent study data and subject motivation as warning signs to alert researchers of the possibility of professional subject enrollment.

Learning Objectives:

1. Identify different types of deceptive strategies that professional subjects may use to fraudulently screen and qualify for clinical trial enrollment.
2. Learn practical protocol design and implementation strategies designed to minimize the risk of professional subject enrollment.

Literature References:

1. Devine EG, Waters ME, Putnam M, Surprise C, O'Malley K, Richambault C, Fishman RL, Knapp CM, Patterson EH, Sarid-Segal O, Streeter C, Colanari L, Ciraulo DA: Concealment and fabrication by experienced research subjects. Clinical Trials: Journal of the Society for Clinical Trials 2013; 10:935–948
2. Devine EG, Peebles KR, Martini V: Strategies to exclude subjects who conceal and fabricate information when enrolling in clinical trials. Contemporary Clinical Trials Communications 2017; 5:67–71

USE OF A GLOBAL RESEARCH SUBJECT DATABASE REGISTRY TO IMPROVE CLINICAL RESEARCH SUBJECT SAFETY AND DATA QUALITY BY PROSPECTIVELY DETECTING, PREVENTING AND ASSESSING PREVENTABLE VIOLATIONS OF INCLUSION AND EXCLUSION CRITERIA

Kerri Weingard, Verified Clinical Trials

Individual Abstract: Inability to reliably verify the clinical research and investigational product history of subjects can result in inclusion/exclusion related protocol violations (IEPVs) including dual enrollment, inappropriate rescreening, attempts at reenrollment, washout period truncation, half-life period violation, and exclusionary compounds or protocols in research history. IEPVs can affect the safety of the subjects and the quality of the data obtained in the

trial (Devine et al., 2013, 2017). Retrospective, self-reported data found three-quarters of admitted professional research subjects (those participating primarily for monetary compensation) admitted to utilizing deceptive behavior, including lying about health conditions, to enter a study (Devine et al., 2013, 2017). Subject deception, forgetfulness or misunderstandings of the inclusion/exclusion (I/E) criteria in relation to their research history – combined with privacy and logistical concerns – results in difficulties confirming subject research history. Without an objective, prospective tool, this can result in otherwise preventable IEPVs. However, the predominance of IEPVs amongst both professional and non-professional research subjects has historically not been well understood. Methods to collect the information were previously retrospective, logistically difficult or unreliable. This paper aims to fill the gap in the literature by utilizing a prospective measure of IEPVs to explore the relationship between IEPVs, the distance subjects travel between research sites, and subjects' attempts to enroll in multiple trials with different health conditions (health condition crossover).

A global research subject database registry utilized at over 1,500 sites in the USA was utilized to prospectively identify IEPVs. Subject partial identifiers were entered after execution of IRB approved consent and IEPVs were identified after authentication and comparison of the subject's research history to the protocol I/E criteria via proprietary algorithm (verification). For this analysis the IEPV data from this database was restricted to subjects verified for CNS trials August 2016 - July 2018. Associations between IEPVs identified during verification, travel distance, and health condition crossovers were assessed (alpha=0.05).

During this time 3,952 subjects were verified into CNS trials. Of these subjects, 1,618 subjects were verified into at least 1 additional trial with any health condition indication, including "healthy volunteer" trials. Among these subjects, 14% traveled to >1 site and 16% had a health condition crossover. Travel between sites was significantly associated with violating I/E criteria. There was a significant association between the distances traveled between verifications and the number of IEPVs identified. There was a significant association between health condition crossovers and violating I/E criteria.

A global research subject database registry prospectively assessed and prevented IEPVs in clinical trials. It provided a much-needed understanding of the relationship between protocol violations and subject behaviors such as distances traveled for clinical trials and attempts at health condition crossover. Given the negative effects of IEPVs on subject safety and data integrity, we argue that the utilization of such a system should be standard clinical practice to simultaneously prevent IEPVs while further the understanding of these issues in clinical trials.

Learning Objectives:

1. Demonstrate utility of a global research subject database for assessment of inclusion/exclusion related protocol violations (IEPVs).
2. Assess the relationship between IEPVs, subject travel distances and subject presentation of health condition.

Literature References:

1. Devine, E. G., Waters, M. E., Putnam, M., Surprise, C., O'Malley, K., & Richambault, C., et al. (2013). Concealment and fabrication by experienced research subjects. Clinical Trials, 10(6), 935-948.
2. Devine, E. G., Peebles, K. R., & Martini, V. (2017). Strategies to exclude subjects who conceal and fabricate information when enrolling in clinical trials. Contemporary Clinical Trials Communications, 5(C), 67-71.

DEFINING A NEW PATIENT BEHAVIORAL CATEGORY: PREVALENCE OF IDENTIFIED CHEATING AND RISK TO STUDY OUTCOMES IN CNS TRIALS

Amanda Paley, AiCure

Individual Abstract: The challenge of deception and fraudulent behavior in clinical trials is receiving increased attention. Fabricating symptoms, nondisclosure of medical conditions, concurrent enrollment, over-reporting of adherence - all contribute to invalidating trial results. Using AI Platforms to capture patient behavioral data allows sponsors to visually confirm study drug ingestion. In addition to measuring traditional non-adherence (dosing holidays, intermittent dosing), the use of AI Platforms allows for the identification of a set of behaviors - distinct from non-adherence - related to patients intentionally cheating and not taking the study drug. This type of fraud is prevalent across therapeutic areas, ranging from 2-30%, but is particularly pronounced in CNS trials where rates of 15%-25% are common. Fraudulent behavior in clinical trials is generally identified early in the study, during the first two weeks. The earlier cheating presents, the more refractory subjects are to interventions and the more likely they are to persist in cheating. Compared to subjects who trigger only one alert, subjects with persistent alerts are twice as likely to early terminate (41% vs 24%), more likely to be male (69% vs 38%), and cheat by removing the pill from their mouth (84% vs. 67%). Identifying fraud in real time allows sponsors to intervene and potentially salvage data quality before the trial is finished and unblinded. Of the subjects identified as cheating, 80% cease contributing poor data or change their behavior (34% early terminate; 46% stop cheating); both improve signal detection. The remaining 20% persist cheating. Trial enrichment strategies such as a placebo lead-in period can be used to identify cheating early on and potentially remove subject's pre-randomization.

Learning Objectives:

1. Participants will gain familiarity with the challenge of cheating behavior in CNS studies.
2. Participants will learn about the value of real-time identification of cheating and the impact on data integrity and trial outcome.

Literature References:

1. Lee CP, Holmes T, Neri E, Kushida CA. Deception in clinical trials and its impact on recruitment and adherence of study participants. Contemp Clin Trials. 2018 Sep;72:146-157.
2. McCann DJ, Petry NM, Bresell A, et al: Medication nonadherence, "professional subjects," and apparent placebo responders: overlapping challenges for medications development. J Clin Psychopharmacol 2015; 35:566-573.
3. Devine EG, Waters ME, Putnam M, Surprise C, O'Malley K, Richambault C, Fishman RL, Knapp CM, Patterson EH, Sarid-Segal O, Streeter C, Colanari L, Ciraulo DA. Concealment and fabrication by experienced research subjects. Clin Trials. 2013;10(6):935-48.

TOWARDS THE IMPLEMENTATION OF PHARMACOGENETICS IN PSYCHIATRY*

Daniel Mueller, University of Toronto

Overall Abstract: Patients often go down a track of trial-and-error with chances of response decreasing and risk of side effects increasing with each subsequent medication. One way to improve treatment response is to use personalized medicine, specifically, pharmacogenomics (PGx). PGx testing, utilizing patient genetic information to guide medication decisions, serves

as a shared decision support tool to add to a provider's toolbox when treating patients. It's critical for providers to have an understanding of what PGx can and can't do for patient care. However, this tool is still in its infancy where education, evaluation, and additional research is crucial. In this panel, we will present the background on what PGx actually is and current guidelines that exist for the science and utilization of PGx information. Specifically, the first speaker, Dr. Michelle Whirl-Carrillo, will review two prominent resources in the field of psychiatric pharmacogenetics: the Clinical Pharmacogenetics Implementation Consortium and the Pharmacogenomics Knowledge Base. Both resources are important in collecting evidence for a variety of drugs relevant in psychiatry for some of which expert recommendations have been provided.

We will also present a critical overview of current commercial tests available for providers as well as best practices for implementation, from benefits to limitations of testing, including the need for standardization and guidelines for testing. In this context, the second speaker, Dr. Sagar Parikh, will present data from a recent large, blinded, RCT evaluating outcomes between PGx-guided care and unguided care in patients with depression. This also lends to a discussion around clinical trial design and evidence for PGx testing. Our third speaker, Dr. Chad Bousman, will provide an overview with examples of current implementation approaches being employed by major medical centers, community health systems, and commercial entities to facilitate the uptake and utilization of PGx testing, emphasizing the pros and cons of each approach. A special emphasis will be given to limitations related to standardization, applicability, and feasibility of PGx testing. The presentation will conclude by summarizing which actionable gene-drug pairs have the highest level of evidence for psychiatric medications, highlighting the most relevant alleles and for which assays with highest analytical validity have become available. Finally, as with all new tools, it's important to understand existing barriers and challenges toward their implementation, including cost-effectiveness of PGx testing, i.e. how PGx can potentially reduce healthcare utilization and cost for patients, payers, and society. The fourth speaker, Dr. Susanne Haga, will address insurance coverage, provider preparedness, and patient-provider communication, areas that have been identified as major barriers to implementation. Understanding of the delivery options, current barriers, and solutions under investigation may help clinicians identify an appropriate strategy to integrate PGx testing in their clinical setting and gain broader awareness about the use of PGx testing.

Our discussant, Dr. Michael Thase, will summarize the four presentations and moderate the discussion between the audience and the presenters.

Overall, we believe that this panel will provide an excellent understanding of the current state of PGx testing in psychiatry, the benefits and limitations of testing, when to consider testing, and the need for additional data demonstrating the utility of testing for widespread use.

Learning Objectives:

1. Understanding principles, scientific evidence, implementation models and barriers of using pharmacogenetics for psychiatric medications.
2. Develop a deeper understanding and applicability of actionable gene-drug pairs as a way to optimize patient treatment.

CPIC AND PHARMGKB REVIEW OF RELEVANT GENE-DRUG PAIRS IN PSYCHIATRIC PHARMACOGENETICS

Michelle Whirl-Carrillo, Stanford University

Individual Abstract: This talk will review two prominent resources in the field of psychiatric pharmacogenetics: the Clinical Pharmacogenetics Implementation Consortium and the Pharmacogenomics Knowledge Base. The Clinical Pharmacogenetics Implementation Consortium (CPIC; https://cpicpgx.org) is an international consortium focused on creating and

publishing evidence-based guidelines for the clinical use of genetic information when prescribing medication. CPIC has published guidelines for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants and selective serotonin reuptake inhibitors. The Pharmacogenomics Knowledge Base (PharmGKB; https://www.pharmgkb.org) is a freely available web-based resource that collects, curates and disseminates knowledge about genotype-phenotype relationships. Specifically, PharmGKB contains curated annotations of gene-drug and variant-drug relationships from the peer-reviewed literature and FDA-approved drug labels. This resource provides broad scientific evidence for a variety of drugs relevant in psychiatry, including but not limited to those that are a focus of CPIC guidelines, ranging from clinically actionable gene-drug pairs to those with preliminary evidence.

Learning Objectives:

1. Learn about the Clinical Pharmacogenetics Implementation Consortium.
2. Learn about the Pharmacogenomics Knowledge Base.

Literature References:

1. Relling MV, Klein TE: CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clin Pharmacol Ther 2011: 89(3):464-7
2. Whirl-Carrillo M, McDonagh EM, Hebert JM, et al: Pharmacogenomics Knowledge for Personalized Medicine. Clin Pharmacol Ther 2012; 92(4): 414-417.

USING COMBINATORIAL PHARMACOGENOMIC TESTING TO PICK MEDICATION FOR MAJOR DEPRESSIVE DISORDER: RESULTS FROM A LARGE, BLINDED, RANDOMIZED CONTROL TRIAL

Sagar Parikh, University of Michigan, Ann Arbor

Individual Abstract: Background: Antidepressant prescribing in Major Depressive Disorder (MDD) is currently limited by lack of clinical or lab biomarkers. Pharmacogenomic (PGx) testing may improve MDD patient outcomes by identifying medications for which safety and efficacy are impacted by genetic composition. Here we present the results of the first prospective, large-scale, patient and rater-blind, randomized control trial evaluating the clinical utility of combinatorial PGx testing to inform medication selection.

Methods: 1,167 MDD outpatients with an inadequate response to ≥1 psychotropic medications were enrolled and randomized 1:1 to Treatment as Usual (TAU) or PGx guided-care study arms. Both arms received combinatorial PGx testing. The combinatorial PGx test report categorized medications in three groups based on the level of gene-drug interactions: (1) 'use as directed', (2) 'use with caution', or (3) 'use with increased caution and more frequent monitoring'. Patient assessments were performed at weeks 0 (baseline), 4, 8, 12, and 24. Patients and raters were blinded in both arms until after week 8. In the PGx guided-care arm, physicians had access to the test report to guide medication selection. In the TAU arm, active treatment was performed by physicians blinded to the combinatorial PGx test report until after week 8. Outcomes utilizing the Hamilton Depression Rating Scale (HAM-D17) were reported at the fully blinded week 8 time point. The primary outcome was symptom improvement (percent change in HAM-D17 from baseline) and the secondary outcomes were response (50% decrease in HAM-D17 from baseline) and remission (HAM-D17 <7). Medications were considered congruent with combinatorial PGx test result if they were in the 'use as directed' or 'use with caution' report categories, while medications in the 'use with increased caution and more frequent monitoring' were considered incongruent. Patients in guided-care and TAU arms who were on one or more incongruent medications at baseline were analyzed separately according to whether they changed to congruent medications by week 8.

Results: At week 8, the primary outcome of symptom improvement for individuals in the guided-care arm was not significantly different than TAU (27% versus 24%, p=0.11).

However, individuals in the guided-care arm were significantly more likely than those in TAU to achieve secondary outcomes of response (26% versus 20%; p=0.01) and remission (15% versus 10%; p<0.01). Congruent prescribing in the guided-care arm increased from 79% to 91% by week 8, while congruent prescribing remained unchanged in the TAU arm. Among patients who were taking incongruent medications at baseline, those who changed to congruent medications by week 8 demonstrated significantly greater symptom improvement (p<0.01), response (p=0.04), and remission rates (p<0.01) compared to those who persisted on incongruent medications.
Conclusions: Medication prescribing decisions guided by combinatorial PGx testing improved patient outcomes for MDD compared to treatment-as-usual. Clinical outcomes were most substantially improved for patients whose medications were identified as incongruent at baseline, allowing change of treatment.

Learning Objectives:

1. Identify what is involved in creating and using a pharmacogenomic test that combines pharmacokinetic and pharmacodynamic information.
2. Review design and outcomes from a large RCT testing the clinical outcome of patients who are randomly assigned to have or not have use of a particular pharmacogenomic test at baseline.

Literature References:

1. Bousman, C.A., Dunlop, B.W., 2018. Genotype, phenotype, and medication recommendation agreement among commercial pharmacogenetic-based decision support tools. Pharmacogenomics J Epub ahead of print, DOI 10.1038/s41397-41018-40027-41393.
2. Bradley, P., Shiekh, M., Mehra, V., Vrbicky, K., Layle, S., Olson, M.C., Maciel, A., Cullors, A., Garces, J.A., Lukowiak, A.A., 2018. Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: A randomized clinical trial demonstrating clinical utility. J Psychiatr Res 96, 100-107.

APPROACHES AND HURDLES TO IMPLEMENTATION OF PHARMACOGENETICS IN PSYCHIATRY

Chad Bousman, University of Calgary

Individual Abstract: Pharmacogenetics (PGx), the study of how genetic variation affects response to pharmacological agents, is an emerging technology positioned to reduce the number of adverse drug reactions, boost efficacy, and ultimately provide cost savings to the healthcare system. This is particularly the case in the delivery of mental health care, where there are 23 commonly used medications for which PGx information either could or should be used to tailor prescribing practice. In fact, two-thirds of people carry at least one actionable (functional) genetic variant relevant to mental health medications. These figures have, in part, stimulated interest and spurred successful efforts to implement PGx testing into routine mental health care. For some however, enthusiasm for the implementation of PGx testing into mental health care has been tempered by concerns related to the standardization, applicability, and feasibility of this testing. In this presentation, I will provide an overview and examples of current implementation approaches being employed by major medical centers, community health systems, and commercial entities to facilitate the uptake and utilization of PGx testing, emphasizing the pros and cons of each approach. I will then highlight how concerns related to standardization, applicability, and feasibility of PGx testing are being addressed and conclude with perspectives on the future of PGx testing implementation in mental health care.

Learning Objectives:

1. To provide an overview of pharmacogenetics implementation approaches.

2. To highlight the key hurdles of implementing pharmacogenetics in psychiatry.

Literature References:

1. Bousman C, Maruf AA, Müller DJ. Towards the integration of pharmacogenetics in psychiatry: a minimum, evidence-based genetic testing panel. Curr Opin Psychiatry. 2018;In press.
2. Bousman C, Dunlop B. Genotype, phenotype, and medication recommendation agreement among commercial pharmacogenetic-based decision support tools. The Pharmacogenomics Journal. 2018;In press.

CHALLENGES IN THE DELIVERY OF PHARMACOGENETIC TESTING

Susanne Haga, Duke University School of Medicine

Individual Abstract: Pharmacogenetic (PGx) testing can inform drug dosing and selection by assessing genetic variants known to impact risks of adverse response or non-effectiveness. Although multiple delivery models for PGx testing are currently being explored or used, it is not clear which models are most effective and can be implemented widely. Furthermore, the availability and delivery of PGx testing, particularly in the outpatient setting, may vary considerably due in part to providers' knowledge and experience with testing. This presentation will provide an overview of delivery models, and barriers to implementation reported in the literature and observed in our own studies. Specifically, the presentation will highlight the current clinical evidence, insurance coverage, provider preparedness, and patient-provider communication, areas that have been identified as major barriers to implementation. Understanding of the delivery options, current barriers, and solutions under investigation may help clinicians identify an appropriate strategy to integrate PGx testing in their clinical setting and gain broader awareness about the use of PGx testing.

Learning Objectives:

1. To learn of current clinical delivery models of pharmacogenetic testing.
2. To understand the current barriers to implementation and solutions under investigation.

Literature References:

1. Danahey K, Borden BA, Furner B, Yukman P, Hussain S, Saner D, Volchenboum SL, Ratain MJ, O'Donnell PH. Simplifying the use of pharmacogenomics in clinical practice: Building the genomic prescribing system. J Biomed Inform. 2017 Nov;75:110-121.
2. Dong OM, Wiltshire T. Advancing precision medicine in healthcare: addressing implementation challenges to increase pharmacogenetic testing in the clinical setting. Physiol Genomics. 2017 Jul 1;49(7):346-354.

ADAPTING TREATMENT OUTCOMES OF MAJOR DEPRESSIVE DISORDER AS RESEARCH EVOLVES: HOW BIOMARKERS, FUNCTIONAL MEASURES, AND ASSOCIATED FEATURES CAN INFORM THE DEFINITION OF RESPONSE AND REMISSION*

Madhukar Trivedi, UT Southwestern Medical Center

Overall Abstract: Background: Reduction in depression severity, often operationalized as response (>50% reduction from baseline) and remission (no or minimal symptom severity), is the gold standard outcome measure for assessing antidepressant treatment efficacy. Per Food and Drug Administration guidelines, currently acceptable measures of symptom severity include either an overall clinical impression or scores on the Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, and Children's Depression Rating Scale.

In addition to missing out on several important symptom domains, these scales are often interpreted on the basis of an overall, total score. Increasing evidence demonstrates that this practice is insufficient to capture the heterogeneity associated with syndromic presentation of depression and the diversity of improved outcomes with effective treatment, thereby preventing our ability to effectively personalize treatment recommendations.
Innovation: This symposium will demonstrate the clinical utility of in-depth measurements of specific symptoms of depression and associated symptomatic and functional domains to tailor treatment(s) on an individual, rather than a population-based level. Broadly, lectures will demonstrate that specific measures of irritability, peripheral biomarkers, cognition, or sleep distribution are associated with treatment outcome and provide meaningful information above and beyond an overall depression symptom score.
Results: Specifically, we will show that early changes in irritability can be used to reliably calculate individual-patient level likelihood of remission versus no meaningful benefit. Baseline levels of c-reactive protein are associated with suicide propensity in a gender-specific manner. Cognitive performance in domains such as executive function, learning, memory, and attention has functional implications that extend beyond symptomatic improvement. Finally, circadian shifts, rather than overall hyper- or insomnia more meaningfully inform treatment response.
Conclusion: In summary, to account for the heterogeneity of depression and accurately assess treatment response, it will be necessary to adapt how we define and quantify markers of dysfunction and recovery.

Learning Objectives:

1. Understand current paradigms used for assessing treatment outcome in depression research.
2. Increase awareness of alternative measures which may more effectively characterize or predict treatment outcome.

CLINICAL UTILITY OF MEASURING IRRITABILITY IN MAJOR DEPRESSIVE DISORDER: PREDICTION OF INDIVIDUAL-LEVEL ACUTE-PHASE TREATMENT OUTCOMES IN TWO SEPARATE SAMPLES OF DEPRESSED OUTPATIENTS

Manish Jha, UT Southwestern

Individual Abstract: Background: While irritability is reported frequently, it is considered a diagnostic symptom only in adolescents but not in adult patients with major depressive disorder (MDD). The goal of this report is to evaluate improvement in irritability with antidepressant treatment and its prognostic utility in treatment-seeking adult outpatients with MDD.
Methods: Mixed model analyses tested baseline-to-week-4 changes in irritability [5-item irritability domain of Concise Associated Symptom Tracking scale (CAST-IRR)] after controlling for depression severity [16-item Quick Inventory of Depressive Symptomatology Clinician-Rated (QIDS-C)] in the Combining Medications to Enhance Depression Outcomes (CO-MED) trial (n=664). An interactive calculator for remission (QIDS-C $\leq$5) and no-meaningful-benefit (<30% QIDS-C reduction from baseline) at week-8 was developed with logistic regression analyses in CO-MED trial using participants with complete data (n=431). Net reclassification improvement analyses were conducted to determine the increase in predictive accuracy by adding irritability to the models that included just baseline and week-4 depression severity. Using the beta estimates from the CO-MED trial models, this calculator was independently replicated in the Suicide Assessment and Methodology Study (SAMS, n=163).

Results: In CO-MED trial, irritability was reduced [effect size (ES)=1.06, p<0.0001] from baseline to week-4. This reduction was significant even after adjusting for QIDS-C change (adjusted ES=0.36, p <0.0001). One standard deviation greater baseline-to-week-4 CAST-IRR reduction predicted 1.73 times higher likelihood of remission (p=0.0001) and 0.72 times lower likelihood of no-meaningful-benefit (p=0.036) at week-8, independent of baseline QIDS-C and CAST-IRR and baseline-to-week-4 QIDS-C reduction. The net reclassification improvement for remission and no-meaningful-benefit were 0.36 [95% confidence interval (CI) 0.17, 0.56; p<0.0001) and 0.34 (95% CI 0.12, 0.57; p=0.004) respectively. With the inclusion of irritability variables in the remission model, 13% of the remitters were correctly reclassified and 23% of the non-remitters were correctly reclassified. Similarly, in the no-meaningful-benefit model, 20% of those with no-meaningful-benefit were correctly reclassified whereas 14% with meaningful-benefit were correctly reclassified with the inclusion of irritability variables.
The model estimates for remission [area under the curve (AUC)=0.795] and no-meaningful-benefit (AUC=0.757) in CO-MED trial were used to predict remission (AUC=0.796) and no-meaningful-benefit (AUC=0.842) in SAMS. With a web-based calculator, users can specify the QIDS-C and CAST-IRR values at baseline and week-4 to obtain estimated probabilities of remission and no-meaningful-benefit at week-8.
Conclusions: Irritability is an important symptom domain of MDD that is not fully reflected in depressive symptom severity measures. Early reductions in irritability when combined with changes in depressive symptom severity provide a robust estimate of an individual MDD outpatient's likelihood of remission or no-meaningful-benefit.

Learning Objectives:

1. Recognize irritability as an important symptom domain in adult outpatients with major depressive disorder.
2. Identify the clinical utility of systematic assessment of irritability and depression severity early in course of antidepressant treatment to predict long-term outcomes.

Literature References:

1. Fava M, Hwang I, Rush AJ, Sampson N, Walters EE, Kessler RC. The importance of irritability as a symptom of major depressive disorder: results from the National Comorbidity Survey Replication. Molecular Psychiatry. 2010;15:856-867.
2. Jha MK, Minhajuddin A, South C, Rush AJ, Trivedi MH. Worsening Anxiety, Irritability, Insomnia, or Panic Predicts Poorer Antidepressant Treatment Outcomes: Clinical Utility and Validation of the Concise Associated Symptom Tracking (CAST) Scale. Int J Neuropsychopharmacol. 2018 Apr 1;21(4):325-332

SEX DIFFERENCES IN ASSOCIATION OF INFLAMMATION AND SUICIDALITY: FINDINGS FROM TWO SEPARATE COHORTS OF PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Cherise Chin Fatt, University of Texas Southwestern Medical Center

Individual Abstract: Background: Role of inflammation in suicidality has gained recent attention. However, it is unclear whether the association between suicidality and inflammation differs on the basis of gender.
Methods: Participants of Establishing Moderators and Biosignatures of Antidepressant Response in Clinical care (EMBARC) study with plasma c-reactive protein (CRP) available at baseline (n=219) were included. Gender-stratified mixed model analyses tested baseline-CRP (categorized as <3 and ≥3 mg/L)-by-visit (weeks-0, 1, 2, 3, 4, 6, and 8) on changes in suicide propensity and ideations (using Concise Health Risk Tracking scale). Data from Combining Medications to Enhance Depression Outcomes (CO-MED) trial were used for replication.

Results: In EMBARC, there was a significant baseline-CRP-by-visit interaction for changes in suicide propensity in males (p=0.046) but not in females (p=0.412) even after controlling for age, race, ethnicity, site, body mass index, and age of onset. While suicide propensity scores were similar at baseline (p=0.751), males with CRP ≥3 mg/L (n=10) at baseline had significantly higher scores at week 8 (p=0.050) than those with CRP <3 mg/L (n=65). Pre-treatment CRP did not predict changes in suicidal ideations in either males (p=0.743) or females (p=0.308). In CO-MED trial, while suicide propensity scores were similar at baseline, males with CRP ≥3 mg/L (n=14) had higher suicide propensity from weeks 6-12 (Cohen's d =0.67-1.34) than those with CRP <3mg/L (n=35).
Conclusion: In a large cohort of depressed outpatients, high baseline CRP predicted persistently elevated suicide propensity after acute-phase antidepressant treatment in males but not in females. These findings were replicated in a separate cohort.

Learning Objectives:

1. Recognize suicide propensity as an important treatment outcome with antidepressant medications.
2. Understand the role of sex and inflammation in predicting changes in suicide propensity with treatment.

Literature References:

1. Jha, M, Trivedi, M: Personalized antidepressant selection and pathway to novel treatments: clinical utility of targeting inflammation. Int J Mol Sci, 2018; 233.
2. Trombello, J, Killian. M, Grannemann, B, et al: The Concise Health Risk Tracking Self-Report (CHRT-SR): Psychometrics within a placebo-controlled antidepressant trial among depressed outpatients.J Psychopharmacol, 2018, In Press.

ASSESSING COGNITIVE PERFORMANCE AS A MARKER OF FUNCTIONAL OUTCOME: RESULTS FROM THE LONGITUDINAL DALLAS 2K STUDY OF DEPRESSIVE DISORDERS

Tracy Greer, University of Texas Southwestern Medical Center at Dallas

Individual Abstract: Depression is known to significantly impair cognition. Both depressive symptoms and cognitive impairments reduce functioning, productivity, and quality of life in depressed individuals. Although cognition can improve in conjunction with depression symptom improvements, data suggest that there is some independence between improvements in cognition and depressive symptoms. This is particularly important given that many depressed individuals have cognitive impairments and functional impairments that remain even when symptomatic remission is achieved. Data were analyzed from initial visits (n=128) for a naturalistic, longitudinal study on depressive disorders, the Dallas 2000 study (D2K). D2K aims to evaluate the long-term course of depression and its treatment, with a specific emphasis on biomarker characterization of depressive subtypes. Depressive symptomatology (measured by the Quick Inventory for Symptomatology, Clinician-Rated version) and cognitive function (measured by with NIH Toolbox Composite, Fluid, and Crystallized Cognition T-scores) were used to predict psychosocial function and work productivity (measured by the Work and Social Adjustment Scale and Work Productivity and Impairment Scale). Lower depressive symptomatology and higher cognitive function were hypothesized to be associated with better functioning and work productivity. Lower depressive symptom severity predicted significantly better functioning and work productivity, but composite cognitive performance did not. However, when cognition was added to the model, the impact of depressive severity was reduced, suggesting that it is meaningfully contributing to functioning and work productivity. This suggests that cognition explains a portion of the relationship between depressive symptom severity and functioning. The complex relationship between depression and cognition and the

impact of that relationship on work and social function highlights several important points that should be further explored: 1) characterization of biological mediators and moderators of this relationship; 2) the impact of treatment type and response on this relationship; and 3) consideration of cognitive and functional outcomes as important targets of treatment efficacy for depression.

Learning Objectives:

1. To understand the relationship between cognition and depressive symptom severity and functioning.
2. To recognize the need for identifying alternative metrics of depression outcome, such as cognitive performance.

Literature References:

1. Greer, T. L., Kurian, B. T., & Trivedi, M. H. (2010). Defining and measuring functional recovery from depression. CNS Drugs, 24(4), 267-284. doi:10.2165/11530230-000000000-00000
2. Jha, M. K., Minhajuddin, A., Greer, T. L., Carmody, T., Rush, A. J., & Trivedi, M. H. (2016). Early Improvement in Work Productivity Predicts Future Clinical Course in Depressed Outpatients: Findings From the CO-MED Trial. Am J Psychiatry, 173(12), 1196-1204. doi:10.1176/appi.ajp.2016.16020176

SLEEP PROBLEMS IN MAJOR DEPRESSIVE DISORDER: ANALYZING DYSFUNCTIONAL PATTERNS TO HELP DETERMINE BIOMARKERS

Brittany Mason, The University of Texas Southwestern Medical Center

Individual Abstract: Change in sleep pattern is a core symptom of depression and is regularly assessed in validated measures of depression. Sleep dysfunction is also one of the earliest symptoms to present in persons who go on to develop a major depressive episode and may be less likely to normalize following depressive episode remission. Sleep disturbances can exacerbate difficulties in many areas of functioning, including cognition, somatic issues, rumination and overall feelings of wellness. However, a nuanced examination of sleep dysfunction and assessment of its overall contribution to symptom burden is not well integrated into depression treatment. Many commonly used assessments for depression capture different aspects of sleep dysfunction, yet rarely examine them comprehensively. Thus, we sought to characterize specific sleep disturbances in the STAR*D study by analyzing 4 items of the Inventory of Depressive Symptoms- Clinician Rating (IDS-C) scale. Using a conceptualization that different patterns of sleep dysfunction (e.g., a circadian shift as compared to hypersomnia or insomnia) could denote different underlying biological contributors, we analyzed various patterns of sleep dysfunction and associated them with clinical symptoms. We first grouped sleep patterns by distinct biologically informed changes and then confirmed distinct groups via cluster analysis. Using sleep pattern dysfunction rather than a single capture of overall sleep disturbance will highlight key biomarkers worthy of study. These biomarkers will likely then help clarify sub-types of depression and provide insight into better diagnostic and treatment options. By considering the casual factors for sleep dysfunction and these distinct groups, we may be able to better target and address a major symptom that causes significant decrease in quality of life for patients with depression, as well as many other mental and physical disorders.

Learning Objectives:

1. To establish the need for specific sleep characterization in MDD
2. To utilize existing sleep assessments to further understanding of MDD sub-types and find key biomarkers

Literature References:

1. Rethorst CD, Greer TL, Toups MS, et al: IL-1β and BDNF are associated with improvement in hypersomnia but not insomnia following exercise in major depressive disorder. Transl Psychiatry 2015: 5:e611.
2. Michaels MS, Balthrop T, Nadorff MR et al: Total sleep time as a predictor of suicidal behaviour. J Sleep Res 2017; 26: 732-738.

NEW MECHANISMS, NEW OPPORTUNITIES: INTEGRATING NOVEL ANTIDEPRESSANTS IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER*

Leslie Citrome, New York Medical College

Overall Abstract: Despite the availability of a large number of antidepressants, people with major depressive disorder (MDD) have unmet treatment needs. Patients being treated for MDD often experience lack of response, delayed efficacy and side effects that cause them to discontinue their medications, and residual symptoms that interfere with functioning. Contributing factors to the continued burden and poor outcomes of MDD include clinicians' failures to (1) consider the biological differences among people living with MDD that affect the way they respond or not to different treatment options, (2) identify how current and future medications with novel mechanisms of action (MOAs) may serve the needs of some individuals better than others because of their particular biological makeup, and (3) measure whether a person's treatment plan is working.

Additionally, although MDD is a life-threatening disease, clinicians often fail to recognize patients at high risk for suicide and patients with comorbidities that can increase mortality risk if left unaddressed. New and emerging antidepressants with novel MOAs, quicker onset, and fewer safety and side effect issues have the potential to improve outcomes for patients with MDD; thus, clinicians must become familiar with their therapeutic profiles, MOAs, and how to effectively use them to help patients achieve remission. To be discussed are the current understanding of the etiology of MDD (including the potential role of novel neurotransmitter systems & receptors), how antidepressants targeted to novel neurotransmitter systems could improve outcomes in patients with MDD and addressing suicide risk.

Learning Objectives:

1. Understand the limitations of currently available antidepressants in the management of major depressive disorder.
2. Understand new mechanisms of action that may effectively target major depressive disorder.

BEYOND THE MONOAMINES: THE ROLE OF DIFFERENT NEUROTRANSMITTERS IN THE ETIOLOGY OF MAJOR DEPRESSIVE DISORDER

James Murrough, Icahn School of Medicine at Mount Sinai

Individual Abstract: Depression is a leading cause of disability worldwide, yet current treatments fall short of what is required to meet this large public health burden. Major advances in basic neuroscience are providing new insights into the fundamental mechanisms of major depressive disorder (MDD), which is envisioned to pave the way for identifying the novel treatment targets of the future. This talk will review the current state of the science concerning the etiology of MDD with an emphasis on novel neurotransmitter systems and receptors as candidate targets for drug discovery. The role of the glutamate system in depression, including the NMDA and AMPA receptors as well as the metabotropic family of receptors, will be

reviewed. The glutamate system is emerging as a rich area for drug discovery based on early discoveries concerning the rapid antidepressant effects of ketamine (a glutamate NMDA receptor antagonist) as well as later phase testing of next generation NMDA receptor modulators. Even more recently, the GABA system is showing itself to be an important system for treatment development with recent advances in clinical studies of novel GABA modulators in MDD. Additional systems with potential important contributions to the etiology of depression that will be discussed include the KCNQ neuro-receptors, the opioid system, and the neuropeptide Y system (NPY). In the case of the KCNQ channel, new basic and translational research showing that this system mediates resilience to stress in rodent depression models and may be a target of therapeutic discovery in humans will be reviewed. To put these transmitter systems in a functional neuroscience context, these systems will be considered in the context of how changes in neurotransmitter function may affect specific circuits in the brain to bring about the specific symptoms of depression.

Learning Objectives:

1. To understand the current state of the field in term of the neurotransmitters and neural systems that are implicated in the etiology of depression
2. To understand how new insights into the basic mechanisms of depression may advance novel antidepressant treatment development

Literature References:

1. Murrough JW, Abdallah CG, Mathew SJ. Targeting glutamate signalling in depression: progress and prospects. Nat Rev Drug Discov. 2017 Jul;16(7):472-486.
2. Tan A, Costi S, Morris LS, Van Dam NT, Kautz M, Whitton AE, Friedman AK, Collins KA, Ahle G, Chadha N, Do B, Pizzagalli DA, Iosifescu DV, Nestler EJ, Han MH, Murrough JW. Effects of the KCNQ channel opener ezogabine on functional connectivity of the ventral striatum and clinical symptoms in patients with major depressive disorder. Mol Psychiatry. 2018 Nov 1. doi: 10.1038/s41380-018-0283-2. [Epub ahead of print]

BEYOND SSRIS AND SNRIS: ARE DRUGS THAT TARGET THE NMDA RECEPTOR, OPIATE SYSTEM, OR MODULATE SEROTONIN 5HT-2A RECEPTORS ON THE HORIZON?

Joseph Goldberg, Icahn School of Medicine at Mount Sinai

Individual Abstract: Putative antidepressant mechanisms of action, like the pathophysiology of depression itself, remain speculative. Psychotropic drug properties do not always align neatly under broad categorical headings – for example, only a few anticonvulsants have been shown to stabilize mood, some but not all second generation antipsychotics alone demonstrably treat depression, and traditional monoaminergic antidepressants show a limited breadth of spectrum for common subtypes such as chronic, bipolar, anxious, or highly recurrent depression. The proposed neuroscience-based nomenclature (NbN) attempts to reframe how we classify a given drug's psychotropic properties based more on a distinct mechanism-by-effect conceptualization rather than broader and more traditional but imprecise categorizations (such as "antipsychotic" or "anticonvulsant" or "analgesic"). In the last 20 years the field has seen enthusiasm rise and fall around promising novel non-monoaminergic antidepressant strategies such as Substance P antagonists, CRF antagonists, and most recently a functional kappa opiate receptor antagonist (buprenorphine plus samidorphan). In the unique case of ketamine and its intranasally administered enantiomer esketamine, burgeoning evidence for acute marked antidepressant effects have drawn attention to modulation of glutamatergic transmission as a possible antidepressant strategy, particularly with respect to NMDA receptor blockade. However, few other NMDA receptor modulators have shown antidepressant

efficacy in preliminary placebo-controlled trials (notably, the glycine partial agonists rapastinel and D-cycloserine). Generalizability about mechanisms to explain ketamine's antidepressant effects remain elusive, in light of failed randomized trials of several other NMDA receptor antagonist drugs (such as riluzole, memantine, lanicemine and traxoprodil), the apparent NMDA-receptor independence of ketamine's active metabolite norhydroxyketamine (involving, instead, AMPA receptor activation), and suspected opioid properties of ketamine (as suggested by naltrexone's blockade of its antidepressant effects). This presentation will discuss new mechanistic approaches to depression pharmacotherapy based on emerging evidence for and against (a) modulation of the glutamate and opioid systems, (b) novel GABAergic compounds (i.e., the GABA-A receptor allosteric modulator brexanolone, found superior to placebo when administered intravenously in postpartum depression), and (c) the possible novel antidepressant role for postsynaptic 5HT2A receptor blockade (suggested by older agents such as mirtazapine (5HT2A Ki ~6 nM) and the newer and more potently binding (5HT2A Ki=0.087 nM) inverse agonist pimavanserin -- shown rapidly to improve depression symptoms better than placebo among SSRI or SNRI inadequate responders in an initial Phase 2 randomized controlled adjunctive trial).

Learning Objectives:

1. To recognize the role of NMDA and other glutamatergic receptor targets as contributing to the antidepressant effects of ketamine and its active metabolites
2. To describe the rationale and efficacy of opiate receptor modulation in the pharmacotherapy of depression

Literature References:

1. Lutz PE, Kieffer BL. Opioid receptors: distinct roles in mood disorders. Trends Neurosci 2013; 36: 195-206.
2. Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. Mol Psychiatry 2018; 23: 801-811.

MAJOR DEPRESSIVE DISORDER, SUICIDE, AND MORTALITY

Bradley Gaynes, University of North Carolina

Individual Abstract: Major Depressive Disorder is a disabling, life-threatening illness, with varying mechanisms of disease. The most notable means of a life-threatening event—suicide—is difficult to identify and manage. While suicidality is common, with 40% of depressed patients expressing suicidal thoughts, attempts and completions, respectively, are much less common. Approximately 15% of those with suicidal ideation attempt suicide at some point in their lives, while 3% of those who attempt will ultimately complete suicide. Effective means to detect and intervene are critical, but elusive. Other less direct but still quite disabling paths, which can increase mortality risk if unaddressed, also exist and challenge the practicing clinician. The morbidity associated with depression, both psychiatric and somatic, is staggering—those with persistent depression have a greater risk of early mortality and die 5 years earlier than those without depression-- yet it remains only partially addressed by available treatments. This presentation will review what is known about effective means to identify and manage these life-threatening complications and highlight key targets for subsequent management strategies.

Learning Objectives:

1. Understand risk of suicide attempts, completed suicide, morbidity, and early mortality in patients with Major Depressive Disorder
2. Understand the current effectiveness of strategies to identify and treat these life-threatening complications

Literature References:

1. Gilman SE, Sucha E, Kingsbury M, Horton NJ, Murphy JM, Colman I. Depression and mortality in a longitudinal study: 1952–2011. Canadian Medical Association Journal. 2017;189(42):E1304-E1310.
2. Otte C, Gold SM, Penninx BW, et al. Major depressive disorder. Nature Reviews Disease Primers. 09/15/online 2016;2:16065.

INTEGRATING THE NEW AND THE OLD: BEST PRACTICES TO ASSESS AND MEASURE SYMPTOMS AND HOW TO BEST INCORPORATE NEW MEDICATION INTERVENTIONS IN CLINICAL PRACTICE

Leslie Citrome, New York Medical College

Individual Abstract: With the plethora of new and innovative medication treatments for the treatment of major depressive disorder comes the responsibility to place these agents into clinical perspective. The advantages and disadvantages of traditional pharmacological interventions are summarized using the evidence-based medicine metrics of number needed to treat (NNT) and number needed to harm (NNH). Depending on available data, similar approaches can be used to appraise the potential of novel interventions. In the care of individuals, measures such as the PHQ-9 can help assess severity of symptoms and ongoing progress (or lack thereof). These measurement tools also serve as a psychoeducational technique to better inform patients about the complex symptomatology of major depressive disorder, help identify residual symptoms, and thus help craft treatment plans that can maximize response, help achieve remission, and reduce the risk of recurrence.

Learning Objectives:

1. Understand how to appraise potential benefits and harms of antidepressant medication treatment using number needed to treat and number needed to harm.
2. Understand the principles of measurement-based care.

Literature References:

1. Citrome L. Vortioxetine for major depressive disorder: An indirect comparison with duloxetine, escitalopram, levomilnacipran, sertraline, venlafaxine, and vilazodone, using number needed to treat, number needed to harm, and likelihood to be helped or harmed. J Affect Disord. 2016;196:225-33.
2. Kurian BT, Grannemann B, Trivedi MH. Feasible evidence-based strategies to manage depression in primary care. . Curr Psychiatry Rep. 2012;14(4):370-5.

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

ASCP EARLY CAREER WORKSHOP: HOW TO GIVE A SCIENTIFIC PRESENTATION

Mirjana Domakonda, Hartford Hospital / Institute of Living

Overall Abstract: The ability to give a scientific presentation is integral to career advancement and success. Giving effective presentations allows academicians and researchers to share their work, foster curiosity, and invite collaboration with colleagues in the broader scientific community. Unfortunately, this crucial skill is rarely taught. This workshop will teach participants how to translate their research findings into a concise and digestible format that will highlight their accomplishments and engage their audiences. Dr. Michael Green will provide participants with a 12-step primer on how to craft a powerful opening statement, organize PowerPoint presentations, and avoid common public speaking pitfalls. Participants

will have an opportunity to hear two early career investigators briefly present their work for constructive commentary and critique on their presentation style and effectiveness. This valuable feedback session and subsequent discussion will provide participants with the knowledge concrete, skills, and confidence to craft their own future successful scientific presentations.

Learning Objectives:

1. Recognize the key elements and of an effective scientific presentation and specific techniques to engage audiences.
2. Demonstrate effective scientific communication styles and identify common presentation pitfalls.

HOW TO GIVE A SCIENTIFIC PRESENTATION

Michael Green, University of California Los Angeles

Individual Abstract: Despite the importance of research presentations for biomedical research careers, investigators typically receive very little training in how to conceptualize, organize, pace, format, and display an effective scientific presentation. Unlike other academic products such as research papers and grants, feedback following presentations tends to be polite rather than constructive. As a result, speakers rarely receive the type of constructive information that helps them to improve their future talks. The goal of this presentation is to provide easily understandable guidelines, strategies, and techniques to enhance the effectiveness of a research talk.

Learning Objectives:

1. To learn how to formulate the optimal structure of a research presentation.
2. To develop techniques to communicate with audiences more effectively.

DURABLE EFFECTS OF PROPOFOL ANESTHESIA ON DEPRESSION, GLUTAMATE, AND GABA

Brian Mickey, University of Utah School of Medicine

Individual Abstract: General anesthetics are powerful modulators of brain function that are used every day to alter consciousness during medical procedures. The neural effects of these agents are typically assumed to be temporary and fully reversible, but recent evidence supports the idea that some general anesthetics can trigger long-lasting neuroplasticity. Ketamine has been investigated intensively over the past decade, but could other general anesthetics be harnessed for therapeutic purposes? Here we describe an initial series of studies designed to assess whether propofol, a general anesthetic that interacts with gamma-aminobutyric acid (GABA) receptors and N-methyl-D-aspartate (NMDA) glutamate receptors, has beneficial effects on mood and depression.

(1) Anecdotally, propofol is reported to cause mood improvements when used for surgery or procedural sedation. We performed a systematic literature review of studies that administered propofol and measured mood states perioperatively. Ten of 14 studies (71%) reported a statistically significant mood improvement after propofol anesthesia. A meta-analysis of 8 studies that compared propofol to other general anesthetics revealed a trend toward more beneficial effects of propofol on self-rated depression (standardized effect size [d] = 2.6; 95%-confidence interval [CI] = 0.15 to 5.4; p = 0.06) but not anxiety (d = 0.86; 95%-CI = 1.2 to 2.9; p = 0.34).

(2) In the first published trial of propofol for depression (Int J Neuropsychopharmacol 21:1079, 2018) we studied 30 subjects (age 18-45, 50% female) with medication-resistant depression. Ten participants each received a series of 10 open-label propofol infusions, and 20 matched

subjects received a series of 10 electroconvulsive therapy treatments. Six of 10 propofol subjects were classified as treatment responders (Hamilton depression scale decrease >50%). Self-rated depression scores improved similarly in the propofol and electroconvulsive therapy groups ($p > 0.20$). During naturalistic follow-up, 5 of the 6 propofol responders remained well for at least 3 months.
(3) We hypothesize that propofol's clinical effects may be mediated through durable changes in GABA and glutamate neurotransmission. To test this idea, we used transcriptome-wide sequencing (RNA-Seq) to measure gene expression from peripheral blood before and after propofol treatment. In addition, proton magnetic resonance spectroscopy was used to serially quantify levels of GABA and glutamate in the medial prefrontal cortex in four subjects. ABAT gene expression increased by 47% ($p = 0.095$), with similar changes observed in propofol responders and non-responders. In contrast, expression of ALDH5A1 changed differentially by response group ($p=0.005$) with a 17% decrease observed among propofol responders. The ratio of glutamate to GABA in prefrontal cortex changed differentially according to response group ($p = 0.017$), decreasing in propofol responders and increasing in non-responders.
In conclusion, these initial studies provide suggestive, but not definitive, evidence that a single propofol exposure can trigger beneficial changes in mood, and that repeated treatments can cause durable improvements in depression. Molecular changes observed in the glutamate-GABA metabolic pathway are consistent with the idea that successful propofol treatment induces a shift from glutamate-predominant excitation toward GABA-predominant inhibition via changes in GABA catabolism. Controlled studies of propofol that integrate GABA- and glutamate-related biomarkers are warranted.

Learning Objectives:

1. Appreciate that general anesthetics can trigger long-lasting changes in brain function.
2. Understand that early pilot studies support the idea that propofol has antidepressant effects.

Literature References:

1. Mickey BJ, White AT, Arp AM, Leonardi K, Torres MM, Larson AL, Odell DH, Whittingham SA, Beck MM, Jessop JE, Sakata DJ, Bushnell LA, Pierson MD, Solzbacher D, Kendrick EJ, Weeks HR 3rd, Light AR, Light KC, Tadler SC (2018). Propofol for Treatment-Resistant Depression: A Pilot Study. Int J Neuropsychopharmacol, 21(12), 1079-1089.
2. Tadler SC, Mickey BJ (2018). Emerging evidence for antidepressant actions of anesthetic agents. [Review]. Curr Opin Anaesthesiol, 31(4), 439-445.

EVIDENCE FOR ALTERED BRAIN REACTIVITY TO NOREPINEPHRINE IN VETERANS WITH A HISTORY OF TRAUMATIC STRESS

Rebecca Hendrickson, VA Puget Sound Health Care System

Individual Abstract: Background: Increases in the quantity or impact of noradrenergic signaling have been implicated in the pathophysiology of posttraumatic stress disorder (PTSD). This increased signaling may result from increased norepinephrine (NE) release, from altered brain responses to NE, or from a combination of both factors. Here, we tested the hypothesis that Veterans reporting a history of trauma exposure would show an increased association between brain NE and mental health symptoms commonly observed after trauma as compared with Veterans who did not report a history of trauma exposure, consistent with increased the possibility of increased brain reactivity to NE after traumatic stress.
Methods: Using a convenience sample of 69 male Veterans with a history of combat-theater deployment, we examined the relationship between trauma-related mental health symptoms and the concentration of NE in cerebrospinal fluid (CSF). Behavioral symptoms associated

with diagnoses of PTSD, depression, insomnia or post-concussive syndrome, which together cover a wide variety of symptoms associated with alterations in arousal systems, such as sleep, mood, concentration, and anxiety, were assessed via self-report and structured clinical interview. Linear regression models were used to quantify the association between CSF NE and symptom intensity in participants with and without a history of trauma exposure, as well as in participants with a history of trauma exposure but who were currently taking the noradrenergic receptor antagonist prazosin.
Results: CSF NE levels were not significantly different as a function of diagnosis or exposure history. Veterans with a history of trauma and who were not using the medication prazosin demonstrated a significantly more positive correlation between CSF NE and behavioral symptom expression than Veterans who had not experienced traumatic stress. However, this pattern was lost in Veterans who had experienced traumatic stress and were taking prazosin at the time of the assessments.
Conclusions: These results are consistent with increased central nervous system responsiveness to noradrenergic signaling in individuals with a history of traumatic exposure, raising the possibility that there may be long-lasting physiologic effects of trauma-exposure that exist independently of whether an individual meets criteria for PTSD at any given point in time. Exploration of the mechanism by which brain responsiveness to NE is modulated following trauma holds the possibility of finding new strategies for both preventing and treating PTSD.

Learning Objectives:

1. In Veterans with a history of exposure to a traumatic stress (but not necessarily a diagnosis of PTSD), higher measured levels of norepinephrine in CSF is associated with increased symptoms such as insomnia and hypervigilance.
2. In Veterans without a history of exposure to a traumatic stress, higher measured levels of norepinephrine in CSF is if anything inversely related to these same symptoms, consistent with the possibility that exposure to a traumatic stress changes the brain reactivity to norepinephrine.

Literature References:

1. Hendrickson RC, Raskind MA, Millard SP, Sikkema C, Terry GE, Pagulayan KF, et al. Evidence for altered brain reactivity to norepinephrine in Veterans with a history of traumatic stress. Neurobiol Stress. 2018;8:103–11.
2. Hendrickson RC, Raskind MA. Noradrenergic dysregulation in the pathophysiology of PTSD. Exp Neurol [Internet]. Elsevier B.V.; 2016 [cited 2016 Jun 2];284:181–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27222130

WHERE DO WE STAND WITH THE USE OF THE SEQUENTIAL PARALLEL COMPARISON DESIGN IN CNS DRUG TRIALS? AN UPDATE 16 YEARS LATER

Maurizio Fava, Massachusetts General Hospital

Overall Abstract: There has been a progressive increase over time in placebo response rates in CNS drug trials. The sequential parallel comparison design (SPCD) was first introduced in 2003 with the goal of reducing both the overall placebo response rate and the sample size of clinical trials, thereby increasing their efficiency and their ability to detect therapeutic signals. The first paper describing SPCD in 2003 has been cited over 330 times in the literature and dozens of papers have proposed or refined analytical approaches to this design. Over 20 multicenter trials using SPCD have been completed in the past 10 years, and over20 CNS multicenter trials are ongoing. In SPCD, the first stage involves an unbalanced randomization between placebo and active treatment, with more patients randomized to placebo to generate a larger cohort of placebo non-responders who then go on to be re-randomized to either staying

on placebo or going on active treatment. The data from all subjects in stage 1 and from placebo non-responders in stage 2 are pooled to provide a more accurate estimation of the treatment effect, without the significant confound of excessive placebo responses. Despite the fact that this design has appealed to biotech and pharma for its putative ability to de-risk trials by reducing the placebo response, several questions raised by regulatory authorities, researchers and scientific reviewers appear to require further clarification for broader acceptance. The goal of this workshop is to discuss some of these issues from a scientific, medical, clinical and statistical viewpoint. Dr. Fava will provide an overview of the background and rationale for the use of SPCD in CNS trials. Dr. Anderson will present a review of the analytical methods developed for SPCD and, in particular, to address the type 1 error. Dr. Laughren will discuss the regulatory issues that emerge in the context of the FDA review of SPCD studies. Dr. Papakostas will present the medical and clinical interpretations of the results of the SPCD trials completed thus far, and Dr. Farchione will serve as the discussant.

Learning Objectives:

1. To become familiar with the background and rationale of the SPCD trails.
2. To understand the advantages and disadvantages of the use of SCPD in CNS clinical trials.

STATISTICAL CONSIDERATIONS IN SEQUENTIAL PARALLEL COMPARISON DESIGNS

Aparna Anderson, Statistics Collaborative, Inc.

Individual Abstract: This presentation will review the statistical methods for analyzing data generated from SPCD trials and provide an overview of the perceived challenges with respect to hypothesis testing as well as interpretation and generalizability of study results.

Learning Objectives:

1. Understand what an SPCD trial is and how it differs from traditional study designs.
2. Understand the implications of SPCD on hypothesis testing and interpretation of study results.

Literature References:

1. Tamura, R. N., & Huang, X: An examination of the efficiency of the sequential parallel design in psychiatric clinical trials. Clinical Trials 2007; 4(4), 309–317.
2. Chen, Y-F, et al: Evaluation of performance of some enrichment designs dealing with high placebo response in psychiatric clinical trials. Contemporary Clinical Trials 2011; Volume 32, Issue 4, 592 - 604.

CLINICAL AND REGULATORY PERSPECTIVE ON UTILIZATION OF SPCD IN REGISTRATIONAL TRIALS

Thomas Laughren, Massachusetts General Hospital Clinical Trials Network and Institute

Individual Abstract: This talk will briefly review the basis for concern about increasing placebo response in registrational trials, relying in part on an exploration of data from FDA databases in MDD and schizophrenia. These data show a trend of increasing placebo response over time and decreasing treatment effect in trials submitted to FDA. Meta-analyses of MDD trials from other investigators shows that higher placebo response rate predicts lower antidepressant-placebo efficacy separation, both for monotherapy and adjunctive trials. Among various approaches to trying to address the increasing lack of success in psychiatry trials is study design, and in particular the SPCD design is intended to specifically address the problem of placebo response.

The focus of this talk will then turn to several practical issues and questions that have been raised in discussions about this design, including:

- Generalizability of results
- Ethical issues
- Where should SPCD be used, and where not?
- Method of randomization for stages 1 and 2
- Weighting of data for stages 1 and 2
- Gaining acceptance by regulatory agencies

Learning Objectives:

1. Understand why it is so critical to address the problem of increasing placebo response in psychiatric drug trials.
2. Understand the role and practical implementation of the SPCD design in psychiatric drug development trials.

Literature References:

1. Chen, Yeh Fong, et al. Evaluation of performance of some enrichment designs dealing with high placebo response in psychiatric clinical trials. Contemporary Clinical Trials 32, 2011, pp 592-604.
2. Baer L and Ivanova A. When should the sequential parallel comparison design be used in clinical trials? Clinical Investigation 3(9), 2013, pp 823-833.

HOW DO ADJUNCTIVE STUDY DESIGNS FOR MDD TRANSLATE INTO CLINICAL PRACTICE?

George Papakostas, Massachusetts General Hospital

Individual Abstract: Clinical trial design for adjunctive treatment of MDD has gone through several iterations. The first-generation design involved randomizing antidepressant partial/non-responders to adjunctive therapy with an experimental agent versus placebo. The main limitation of this approach is relatively high placebo response rates. The second-generation design involves prospectively treating MDD subjects with an antidepressant (along with placebo), then randomizing partial and non- responders to adjunctive therapy with the experimental agent versus placebo. The main advantage of this design is lower placebo response rates, albeit at the expense of double to quadruple sample size requirements compared to its predecessor. The third-generation design, the Sequential Parallel Comparison (SPC) approach, is essentially a hybrid of the first- and second-generation design, aimed at preserving low placebo response rates with far fewer subjects. In this talk, we will address common questions of medical and clinical nature raised over the years by reviewers and regulators using real-world study results, with an aim of placing study design in a clinical perspective.

Learning Objectives:

1. By the end of this talk, the audience will better understand how and why trial designs evolved in this treatment area.
2. By the end of this talk, the audience will better understand how different trial designs translate into clinical practice using real-world study results.

Literature References:

1. Iovieno N, Papakostas GI. Does the presence of an open-label antidepressant treatment period influence study outcome in clinical trials examining augmentation/combination strategies in treatment partial responders/nonresponders with major depressive disorder? J Clin Psychiatry. 2012;73(5):676-83.
2. Papakostas GI, Iovieno N. The nature of placebo response in clinical studies of major depressive disorder. J Clin Psychiatry. 2015;76(4):456-66.

NEGOTIATION STRATEGIES FOR PROFESSIONALS IN CNS RESEARCH: A MID-CAREER MENTORING WORKSHOP*

David Kupfer, University of Pittsburgh School of Medicine/Western Psychiatric Institute and Clinic

Overall Abstract: Negotiation and communication strategies for mid-career professionals in academia or industry are the focus of this third ASCP mid-career workshop. Seasoned mentors from academia and VA research settings offer a lively and engaged discussion on styles of negotiation, preparation for a meaningful meeting, and communication choices. A balance of assertiveness, empathy, flexibility, social intuition is essential to advancing your career through collaborative negotiation with chairs and directors of programs. The evolution from post-doctoral training to first faculty appointment and first grant award does not happen overnight and requires intentional discernment and mentoring. Promotion and advancement that leads to tenure or independent investigator status is secured by self-advocacy and a high regard for reputation and integrity. Divorcing one's early-career mentor may be necessary and requires a delicate dance of negotiation and communication. Learning how to facilitate a healthy dialogue with a chair or director, while showing an understanding of resource limits without projecting a sense of withholding, will be discussed. Steps towards effective leadership and tactics in the supervision of others will be offered. Audience participation is highly encouraged throughout the workshop.

Learning Objectives

1. After the participating in this workshop, the attendee will have a better appreciation for effective communication and negotiation strategies.
2. The attendee will be able to name three or more important features used in negotiating with a chair or director (assertiveness, empathy, flexibility, social intuition, and ethicality).

Literature References:

1. Schneider, Andrea Kupfer and Kupfer, David. Smart & Savvy: Negotiation Strategies in Academia. Meadows Communications LLC, 2017.
2. Davis, L. L., Little, M. S., & Thornton, W. L. (1997). The art and angst of the mentoring relationship. Academic Psychiatry, 21(2), 61-71.

ASCP-ISBD WORKSHOP: UPDATE ON TREATMENT OF BIPOLAR DISORDER*

Trisha Suppes, Stanford University

Overall Abstract: In this workshop we will provide updates on current and emerging treatments in bipolar disorder, as well as a discussion of controversies in the treatment of bipolar disorder. Bipolar depression is a significant unmet need in patients with bipolar disorder. Neurostimulation may show unique support in the management of bipolar depression. Scott Aaronson will explore current evidence from studies on vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and direct current stimulation (DCS). The use of antidepressants in the treatment of bipolar disorders will be reviewed by Trisha Suppes, with a focus on recent studies and recently released guidelines. One element of the ongoing controversy regarding the use of antidepressants in bipolar disorder is a consideration of the differences between bipolar I and II response to antidepressants. Michael Berk will speak on novel therapies for bipolar disorder. These include novel internet psychosocial approaches, re-purposed medications, nutraceutical and mitochondrial approaches with potential efficacy in bipolar disorder. Our last talk will be provided by Roger McIntrye whom will focus on applications of precision medicine to the treatment of bipolar disorder, including recently

completed studies with anti-inflammatory agents. We plan on a brief question and answer period after each talk and time at the end for a panel discussion between the speakers and the audience.

Learning Objectives:

1. Review of new treatments available for bipolar depression.
2. Review of new studies in the use of antidepressants for bipolar disorder.

NEUROSTIMULATION IN THE MANAGEMENT OF BIPOLAR DEPRESSION

Scott Aaronson, Sheppard Pratt Health System

Individual Abstract: Bipolar depression presents a difficult to treat condition. The brain is as much electrical as it is chemical, yet the majority of somatic interventions for bipolar disorder are chemically based. Medications have proven more effective for the management of manic and not depressive symptoms. FDA approved medications for bipolar depression include three atypical antipsychotics, one in combination with an antidepressant. Controversy abounds with regard to the use of antidepressants in bipolar disorder. Neurostimulation techniques may provide a unique option for the management of bipolar depression. There is emerging evidence that Transcranial Magnetic Stimulation (TMS) may provide relief in acute bipolar depression and Vagus Nerve Stimulation (VNS) may be useful in long term management. Data on Direct Current Stimulation (DCS) have shown some conflicted results with efficacy.

A retrospective analysis of 39 bipolar depressed patients receiving left dorsolateral prefrontal cortex stimulation at 10HZ for 4 seconds, every 30 seconds for 37.5 minutes demonstrated a 69% response rate by MADRS criteria and a 35% remission rate with better results in the bipolar I than the bipolar II population (72% vs. 67% response rate). While these are preliminary, open label results, they are consistent with other studies in the field and may represent an opportunity to provide targeted, episode driven, non-systemic support for acute bipolar depressive episodes. A meta-analysis of randomized clinical trials of TMS in bipolar depression supports the use of either left sided high frequency or right sided low frequency stimulation but not bilateral stimulation.

A large naturalistic study of patients with severe treatment resistant depression compared the use of VNS vs. treatment as usual (TAU). This 800-patient study included 117 patients with bipolar depression, 94 of them received VNS and 23 received treatment as usual. These patients failed at least 4 antidepressants and an average of 8. The cumulative response rate over a five-year period was 70.5% for the VNS group and 37.6% for the TAU group with a calculated NNT=3.

There is preliminary evidence that TMS may provide important support for bipolar depressive episodes though this needs to be proven with randomized sham-controlled trials with consistent treatment paradigms. Evidence for the utility of VNS for the chronic management of bipolar depression in a large population suggests it should be more available for use given that it is an FDA approved indication.

Learning Objectives:

1. Describe the potential advantages a neurostimulation paradigm may have over pharmacotherapy in the management of bipolar depression.
2. Differentiate course of treatment between long term strategies (VNS) and short-term strategies (TMS).

Literature References:

1. Aaronson ST, Sears P, Ruvuna F, Bunker M, Conway CR, Dougherty DD, Reimherr FW, Schwartz TL, Zajecka JM. A 5-Year Observational Study of Patients With Treatment-Resistant Depression Treated With Vagus Nerve Stimulation or Treatment

as Usual: Comparison of Response, Remission, and Suicidality. Am J Psychiatry. 2017 Jul 1;174(7):640-648.
2. McGirr A, Karmani S, Arsappa R, et al: Clinical efficacy and safety of repetitive transcranial magnetic stimulation in acute bipolar depression. World Psychiatry 2016. 15(1):85–86.

TREATMENT OF BIPOLAR DEPRESSION: USE OF ANTIDEPRESSANTS AND RECENT GUIDELINE RECOMMENDATIONS

Trisha Suppes, Stanford University

Individual Abstract: Bipolar disorder is characterized by depression as a dominant state for most patients. For many patients it is depression that becomes the common final pathway later in the course of illness, and, in conjunction with mixed symptoms, associated with suicide and life dysfunction. While newer medications such as atypical antipsychotics may be helpful for particularly bipolar I depression, antidepressants are still in common use. This talk will focus on the use of antidepressants for patients with bipolar I or II disorder. A recent study, though not placebo-controlled in patients with bipolar II disorder found no greater efficacy of an SSRI from Lithium and greater drop-out with a combination treatment (Altshuler et al., 2017). Older studies and more recent work, as well as unanswered questions will be discussed, including an ongoing debate about longer term use of antidepressants for patients with bipolar disorder. The most recent treatment guidelines for use of antidepressants in bipolar disorder, including CANMAT, will be reviewed.

Learning Objectives:

1. Understand the pros and cons of using antidepressants for the treatment of bipolar depression.
2. Learn what recent treatment guidelines recommend for the use of antidepressants for treatment of bipolar depression.

Literature References:

1. Yatham L, Kennedy S, Parikh S, Schaffer A, Bond D, Frey B, Sharma V, Goldstein B, Rej S, Beaulieu S, Alda M, MacQueen G, Milev R, Ravindran A, O'Donovan C, McIntosh D, Lam R, Vazquez G, Kapczinski F, McIntyre R, Kozicky J, Kanba S, Lafer B, Suppes T, Calabrese J, Vieta E, Malhi G, Post R, Berk M. Canadian Network for Mood and Anxiety Treatments (CANMAT)/International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disorders. 13 March 2018
2. Altshuler L, Sugar C, McElroy S, Calimlim B, Gitlin M, Keck P, Aquino-Elias A, Martens B, Fischer E, English T, Roach J, Suppes T. Switch rates during acute treatment for bipolar II depression with lithium, sertraline or the combination for bipolar II depression: a randomized, double-blind comparison. Am J Psychiatry. January 2017 174:3, 266-276

NOVEL THERAPIES FOR BIPOLAR DISORDER

Michael Berk, Deakin University

Individual Abstract: The emerging evidence that inflammatory and oxidative processes, altered neurogenesis and mitochondrial dysfunction are increasingly thought to be important in the aetiology and progression of bipolar disorder. The presence of increased inflammatory activity, oxidative stress, mitochondrial dysfunction as well as altered neurogenesis in bipolar disorder has deleterious sequelae that include lipid peroxidation, DNA fragmentation, telomere shortening, protein carbonylation, reduced neurogenesis and vulnerability to apoptosis and

hence structural and cognitive changes. These pathways are potentially druggable and suggest novel therapeutic opportunities. Many of the potential agents are repurposed, and thus have established tolerability and safety profiles. These include N acetylcysteine, aspirin, minocycline, infliximab, celecoxib and statins. Mitochondrial dysfunction also offers potential targets, with the first trial in bipolar disorder completed. Some anti-inflammatory agents such as aspirin may have as preventive potential as part of integrated preventive programs targeting non-communicable disorders. These biological strategies are buttressed by novel psychosocial therapies, especially in the digital domain. This presentation will focus on these novel treatment findings which augment existing approaches in bipolar disorder and hopefully contribute to better outcomes in the disorder.

Learning Objectives:

1. To note the novel biological pathways operating in bipolar disorder.
2. To explore the potential utility of agents operating on these pathways.

Literature References:

1. Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, Yücel M, Gama CS, Dodd S, Dean B, Magalhães PV, Amminger P, McGorry P, Malhi GS. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev. 2011;35(3):804-17.
2. Data-Franco J, Singh A, Popovic D, Ashton M, Berk M, Vieta E, Figueira ML, Dean OM. Beyond the therapeutic shackles of the monoamines: New mechanisms in bipolar disorder biology. Prog Neuropsychopharmacol Biol Psychiatry. 2017;72:73-86.

INFLAMMATION/METABOLIC MEDIATORS OF PSYCHOPATHOLOGY IN MOOD DISORDERS

Roger McIntyre, University of Toronto, University Health Network

Individual Abstract: Disturbance in inflammation and metabolism are well described in individuals with mood disorders. Central disturbances in these foregoing effector systems are implicated in the phenomenology of anhedonia, cognitive impairment, and physical symptoms. This presentation will briefly summarize extent literature on this topic and will introduce novel approaches to attenuate psychopathology in mood disorders targeting inflammation and metabolism.

Learning Objectives:

1. Identify two molecular targets involved in metabolism/inflammation homeostasis relevant to disease processes in mood disorders.
2. To introduce two proof of concept studies supporting the notion that targeting metabolism and inflammation is disease modifying in mood disorders.

Literature References:

1. Rosenblat, J.D., McIntyre, R.S. Bipolar Disorder and Immune Dysfunction: Epidemiological Findings, Proposed Pathophysiology and Clinical Implications. (2017) Brain Sci.
2. McIntyre, R.S. Is Obesity Changing the Phenotype of Bipolar Disorder From Predominately Euphoric Towards Mixed Presentations? (2018) Bipolar Disord.

Thursday, May 30, 2019

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

INNOVATIONS IN PERSONALIZED MEDICINE: FROM BIOMARKERS TO PATIENT-CENTERED CARE
Madhukar Trivedi, UT Southwestern Medical Center

Overall Abstract: In contrast to the rest of medicine, psychiatric conditions are still considered behavioral or emotional conditions, implying that both our diagnostic and treatment strategies rely solely on clinical symptom presentation. As such, treatment recommendations are traditionally given without factoring individual variability in biological factors, such as genes, brain structure and function, or other factors beyond symptom clusters. As a result, treatments for psychiatric conditions remain largely trial and error, and most of our disorders have very low remission rates across treatment strategies. It is time for us to take move Psychiatry into the modern age of precision medicine, where we take a comprehensive look at the complex interplay between clinical and biological phenotypes. Identification of clinical and biological markers that can predict treatment outcomes will be crucial, and with recent technological advances in machine learning and computational systems, we are perfectly situated to make great strides in our treatments. Some of these steps have already begun through large trials in depression, bipolar disorder, and schizophrenia, among others. This presentation will focus on major depressive disorder as an example of strides we are making in towards precision medicine.

THE ALL OF US RESEARCH PROGRAM: OPPORTUNITIES FOR MENTAL HEALTH RESEARCH
Jordan Smoller, Massachusetts General Hospital & Harvard Medical School

Individual Abstract: Neuropsychiatric disorders are the leading cause of disability worldwide and are responsible for an enormous burden of suffering for affected individuals and their families. They are also associated with substantial medical comorbidity and even mortality (related to suicide and comorbid disease). While effective therapies are available, too often treatment is ineffective or poorly tolerated, and current approaches to diagnosis and treatment are still rooted in insights that are decades old. The NIH All of Us Research Program (AoURP) will gather a diverse array of data types for a longitudinal cohort of unprecedented scale and scope. As such, the AoURP represents an opportunity to transform research in all areas of medicine including mental health and substance use. This presentation will provide an overview of plans for data collection relevant to psychiatric and substance use phenotypes, including participant surveys, electronic health records, digital health technologies, and genomics. In addition, the presentation will preview plans for access and use of AoURP by the scientific community as well as potential applications of these data relevant to psychiatric phenotypes.

Learning Objectives:
At the conclusion of this presentation, attendees will be able to:

1. Summarize the plans for mental health and substance use data collection in the All of Us Research Program.
2. Describe how data collected through the AoURP can be accessed by the research community.

Literature References:

1. Smoller JW. The use of electronic health records for psychiatric phenotyping and genomics. Am J Med Genet B Neuropsychiatr Genet. 2018 Oct;177(7):601-612. doi: 10.1002/ajmg.b.32548. PMID: 28557243
2. Stein MB, Smoller JW. Precision Psychiatry-Will Genomic Medicine Lead the Way? JAMA Psychiatry. 2018 Dec 1;75(12): 1303.doi:10.1001/jamapsychiatry.2018.0375. PMID: 29800947

CURRENT STATUS OF ALL OF US RESEARCH PROGRAM

Holly Garriock, National Institutes of Health

Individual Abstract: The time during this presentation will be spent providing an overview of the All of Research Program, including an update on the current status, how researchers and clinicians might benefit from the program, and what the future plans of the program are.

Learning Objectives:

1. Be knowledgeable of what the All of Us Research Program is.
2. Know the current status of the All of Us Research Program.
3. Know how the All of Us Research Program could be useful to you as researchers and clinicians.
4. Know the plans for future development of the All of Us Research Program.

THE MILLION VETERAN PROGRAM: A LONGITUDINAL COHORT OF U.S. VETERANS FOR GENETIC AND EPIDEMIOLOGICAL RESEARCH

Sumitra Muralidhar, Department of Veterans Affairs

Individual Abstract: The Department of Veterans Affairs' Million Veteran Program (MVP) is one of the world's largest longitudinal cohorts collecting clinical, genetic, lifestyle and military exposure information from at least one million Veterans. Currently, over 740,000 Veterans have enrolled. MVP is a highly diverse cohort with roughly 18% African Americans and 7% Hispanics represented. Baseline genotype data using a customized Affymetrix biobank chip is generated on every participant. Roughly thirty scientific studies are currently approved/underway as alpha, beta and gamma test projects. Mental health topics under investigation include PTSD, schizophrenia and bipolar disorder, suicide risk, multi-substance abuse and pharmacogenomics of opioid agonists. An overview of the program infrastructure, plans for future data access, representative scientific findings, and implications for precision medicine will be presented.

Learning Objective:

1. Knowledge of a national resource for genetic and epidemiologic studies.

Literature Reference:

1. Gaziano JM et al. Million Veteran Program: A mega-biobank to study genetic influences on health and disease. J. Clin. Epid. 2016 Feb;70:214-23.

THE ADOLESCENT BRAIN COGNITIVE DEVELOPMENT (ABCD) STUDY: AN OPEN SCIENCE DATA RESOURCE

Katia Howlett, National Institutes of Health, National Institute of Drug Abuse

Individual Abstract: The Adolescent Brain Cognitive Development (ABCD) study is a multi-site longitudinal study of more than 11,000 youth starting at age 9-10 designed to increase our understanding of how diverse experiences influence adolescent development. Youth and their families complete comprehensive assessments of physical and mental health, substance use, environment, and cognitive function as well as biospecimen collection and structural and

functional brain imaging. An outline the study design, the demographic characteristics of the cohort, and emerging findings about the influence of environmental factors and gene by environment interactions on brain, cognitive, and psychological development will be presented. This valuable dataset will be made rapidly available to the scientific community through the National Institute of Mental Health Data Archive, allowing scientists worldwide to conduct analyses, pool resources, and enrich the value of this study.

Learning Objective:

1. Participants will learn about the ABCD Study, how to access the Data, and about the various Data Analyses opportunities.

Literature Reference:

1. Volkow, N.D., Koob, G.F., Croyle, R.T., Bianchi, D.W., Gordon, J.A., Koroshetz, W.J., Pérez-Stable, E.J., Riley, W.T., Bloch, M.H., Conway, K., Deeds, B.G., Dowling, G.J., Grant, S., Howlett, K.D., Matochik, J.A., Morgan, G.D., Murray, M.M., Noronha, A., Spong, C.Y., Wargo, E.M., Warren, K.R., Weiss, S.R.B. (in press). The conception of the ABCD study: From substance use to a broad NIH collaboration. Developmental Cognitive Neuroscience, Available online 10 October 2017.

Federal Agency Updates Plenary
10:00 a.m. - 12:30 p.m.

FEDERAL AGENCY UPDATES PLENARY

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

Overall Abstract: Terri Gleason will discuss psychopharmacology research in the Department of Veterans Affairs. George Koob, National Institute on Alcohol Abuse & Alcoholism, will discuss what science can tell about the treatment of alcohol use disorders. Bruce Cuthbert will discuss an NIMH update on personalized medicine. Kurt Rasmussen, NIDA, will discuss opportunities and challenges in addiction research. Thomas Clarke will discuss a SAMHSA update on the 21st Century Cures Act. Christopher Austin, NCATS, will discuss catalyzing translational innovation.

PSYCHOPHARMACOLOGY RESEARCH IN THE DEPARTMENT OF VETERANS AFFAIRS

Terri Gleason, U.S. Department of Veterans Affairs

Individual Abstract: VA's Office of Research and Development has a long history of supporting psychiatric research particularly focused on advancing treatment for Veterans across topics. This session is intended to provide an overview of our VA research program with the intent to provide participants with details regarding priorities, goals and objectives related to psychopharmacology research. The VA funders' perspective on research areas in need of further research as well as specific initiatives will be presented, and will include some valuable research resources that are unique to VA including the Cooperative Studies program for definitive clinical trials, our translational pathway extending across the research spectrum, Veteran specific data for research, and the Million Veteran Program - all focused on improving patient care by advancing knowledge through scientific evidence.

Learning Objective:

1. Participants should become familiar with the VA Research enterprise, whether internal to VA or external, the possible resources available for research and the ways in which scientific collaboration can be supported.

Literature Reference:

1. www.research.va.gov

WHAT SCIENCE CAN TELL ABOUT THE TREATMENT OF ALCOHOL USE DISORDERS: VIEW FROM THE DARK SIDE

George Koob, National Institute on Alcohol Abuse & Alcoholism

Individual Abstract: Alcohol use disorders cause an enormous amount of human suffering, loss of productivity and cost to our medical care system and the nation's economy. Advances in the science of alcohol use disorders can lead the way to better diagnosis, treatment and prevention of this significant public health problem. Understanding developmental trajectories provides fundamental knowledge of vulnerability to alcohol pathology across the lifespan. Conceptualizing alcohol use disorder from a heuristic framework a binge/intoxication stage, a withdrawal/negative affect stage, and a pre-occupation/anticipation (craving) stage representing the domains of incentive salience, negative emotional states and executive function has allowed identification of key neurocircuits that underlie addiction to alcohol. Basic mechanisms of organ pathology have similarly advanced our knowledge of vulnerability and resilience to organ damage. Such a knowledge base provides the heuristic framework for the development of novel, science-based approaches to diagnosis, prevention and treatment of alcohol use disorders, including medication development, and will facilitate the implementation evidence-based practice in primary care, mental health, and other health care settings.

Learning Objective:

1. To understand how negative reinforcement drives the motivation for compulsive alcohol use in AUD and its implications for treatment.

Literature References:

1. Koob GF. Negative reinforcement in drug addiction: the darkness within. Current Opinion in Neurobiology, 2013, 23:559-563
2. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry, 2016, 3:760-773.

PERSONALIZED MEDICINE: NIMH UPDATE

Bruce Cuthbert, NIH/NIMH

Individual Abstract: This presentation is intended to provide an update regarding NIMH's current research priorities, and how programs concerning precision medicine relate to these priorities. Overall, three of the major clinical and research priorities for NIMH involve reducing rates of suicide, developing new knowledge about neural circuit activity as related to mental disorders, and accelerating progress in computational psychiatry to facilitate the understanding of relationships among high-dimensional data with and across such areas of measurement as genomics, neural circuit activity, behavior, and clinical phenomenology. The presentation will discuss NIMH activities directed toward fostering these goals, including progress toward new approaches in diagnostics and treatment.

Learning Objective:

1. After the presentation, attendees should be able to discuss the priorities for NIMH regarding precision medicine, and how these priorities align with major Institute goals.

Literature Reference:

1. Ferrante M, Redish AD, Oquendo MA, Averbeck BB, Kinnane ME, Gordon JA. Computational psychiatry: A report from the 2017 NIMH workshop on opportunities and challenges. Molecular Psychiatry 2018:doi.org/10.1038/s41380-0063-z.

OPPORTUNITIES AND CHALLENGES IN ADDICTION RESEARCH
Kurt Rasmussen, NIDA

Individual Abstract: Recent scientific advances have increased our understanding of the biological, developmental, and environmental factors involved in drug abuse and addiction and are stimulating further explorations into increasingly targeted strategies for their prevention and treatment. This presentation will highlight a selection of recent scientific advances, provide an update on a number of relevant policy and research initiatives currently being supported by the National Institutes of Health and the National Institute on Drug Abuse, and describe some of the most pressing challenges currently confronting the drug abuse and addiction field and solutions that show promise in effectively addressing them.

Learning Objectives:

Attendance at this presentation will increase participants' awareness of:

1. Illustrative examples of recent research advances in the science of addiction.
2. Current and emerging opportunities for research in drug abuse and addiction related areas both at NIDA and at the NIH.
3. Several of the most pressing challenges currently facing the drug abuse and addiction field and steps being taken to address them.

Literature Reference:

1. Rasmussen K, White DA, Acri JB: NIDA's Medication Development Priorities in Response to the Opioid Crisis: Ten Most Wanted. Neuropsychopharmacol 2019 (in press).

21ST CENTURY CURES ACT: SAMHSA UPDATE
Thomas Clarke, SAMHSA

Individual Abstract: This presentation will provide an update on the Substance Abuse and Mental Health Services Administration (SAMHSA)'s portfolio. Specifically, it will discuss the recent 21 Center Cures Act, which reauthorized SAMHSA and puts great emphasis on evidence-based programs and evaluation. The implementation of the Interdepartmental Serious Mental Illness Coordinating Committee (ISMICC), which coordinates federal mental health efforts as part of the Cures Act, will also be discussed. Finally, data will be presented from SAMHSA's National Study on Drug Use and Health (NSDUH) to highlight recent trends in substance abuse and mental health disorders in the United States. Specific emphasis will be placed on data related to co-occurring and serious mental illness as well as SAMHSA's repose to these issues.

Learning Objective:

1. To understand recent data and trends on mental illnesses from SAMHSA's National Survey on Drug Use and Health data source.

Literature References:

1. Substance Abuse and Mental Health Services Administration. (2018). Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration

CATALYZING TRANSLATIONAL INNOVATION

Christopher Austin, National Institutes of Health, National Center for Advancing Translational Sciences

Individual Abstract: The process by which observations in the laboratory or the clinic are transformed into demonstrably useful interventions that tangibly improve human health is frequently termed "translation." This multi-stage and multifaceted process is poorly understood scientifically, and the current research ecosystem is operationally not well suited to the distinct needs of translation. As a result, biomedical science is in an era of unprecedented accomplishment, particularly in the emerging realm of precision medicine, without a concomitant improvement in meaningful health outcomes, and this is creating pressures that extend from the scientific to the societal and political. To meet the opportunities and needs in translational science, NCATS was created as NIH's newest component in December 2011, via a concatenation of extant NIH programs previously resident in other components of NIH. NCATS is scientifically and organizationally different from other NIH Institutes and Centers. It focuses on what is common to diseases and the translational process and acts a catalyst to bring together the collaborative teams necessary to develop new technologies and paradigms to improve the efficiency and effectiveness of the translational process, from target validation through intervention development to demonstration of public health impact. This talk will provide an overview of NCATS mission, programs, and deliverables, with a view toward ongoing developments in precision medicine.

Learning Objective:

1. To differentiate between the process of "Translation" and the field of "Translational Sciences".

Literature Reference:

1. P. Austin, Christopher. (2018). Translating translation. Nature Reviews Drug Discovery. 17. 10.1038/nrd.2018.27.

Clinical Updates in Psychopharmacology*
2:00 p.m. - 3:30 p.m.

CLINICAL UPDATES IN PSYCHOPHARMACOLOGY SESSION*

Erika Saunders, Penn State College of Medicine, Penn State Milton S. Hershey Medical Center

Overall Abstract: Jennifer Payne, Johns Hopkins School of Medicine, will begin by discussing the psychopharmacology of perinatal depression. Gary Small, David Geffen School of Medicine at UCLA, will then discuss diagnosing dementia vs. delirium vs. depression in the elderly. Ivan Montoya, NIDA, will then discuss medications to prevent and treat opioid use disorders and overdose.

PSYCHOPHARMACOLOGY OF PERINATAL DEPRESSION

Jennifer Payne, Johns Hopkins School of Medicine

Individual Abstract: Perinatal depression is common and potentially life-threatening. The proper management of depression during the perinatal time-period remains controversial, though there is more and more data to support the safe use of antidepressants and other psychiatric medications during pregnancy and lactation. This presentation will discuss the current literature on the safety of antidepressant use during pregnancy and lactation, the risks

of untreated maternal depression and new approaches to the treatment of postpartum depression.

Learning Objectives:

1. Define the term "confounded by indication".
2. Define the difference between relative and absolute risk.
3. Quantify the risk of persistent pulmonary hypertension in antidepressant-exposed newborns.
4. Identify two risks of untreated psychiatric illness during pregnancy.

Literature References:

1. Osborne LM, Payne JL. Depression and Anxiety Monograph. In: Clinical Updates in Women's Health Care. American College of Obstetrics and Gynecologists (Edited by Snyder), 2017.
2. Payne JL. Recent advances and controversies in peripartum depression. Current Obstetrics and Gynecology Reports. 2016; 5:250-56.

DIAGNOSING DEMENTIA VS. DELIRIUM VS. DEPRESSION IN THE ELDERLY

Gary Small, David Geffen School of Medicine at UCLA

Individual Abstract: Age is the greatest single risk factor for developing dementia, a cognitive impairment that makes the patient dependent on others. Despite the availability of standard diagnostic criteria for dementia, several other common clinical syndromes, particularly delirium and depression, frequently overlap. This presentation will review some of the challenges in accurate diagnosis of these conditions and offer a practical strategy for clinical assessment.

Learning Objectives:

Attendees will learn to:

1. Differentiate dementia from delirium and depression in older adults.
2. Apply a systematic strategy for accurate diagnosis of age-related cognitive and mood conditions.

Literature References:

1. Small GW. Detection and prevention of cognitive decline. American Journal of Geriatric Psychiatry. 2016;24:1142-1150.
2. Blackburn P, Wilkins-Ho M, Wiese B. Depression in older adults: Diagnosis and management. BCMJ. 2017;59:171-7.

MEDICATIONS TO PREVENT AND TREAT OPIOID USE DISORDERS AND OVERDOSE

Ivan Montoya, National Institute on Drug Abuse

Individual Abstract: It is estimated that in 2017 more than 2 million people in the United States reported having Opioid Use Disorder (OUD) and almost 40,000 people died from opioid overdose. The pharmacotherapies currently approved by the FDA to treat Opioid Use Disorders (OUDs) and opioid overdose often have suboptimal efficacy or medical safety concerns. This epidemic demands innovative new approaches to prevent and treat these conditions. Significant efforts are being made to expedite the development of medications to prevent and treat OUD and overdose at the pre-clinical and clinical level. They include new medications, new formulations of approved medications as well as biologics such as vaccines and monoclonal antibodies. Some of the therapeutic targets include: prevention of the initiation of OUD, reduction of severity of OUDs, improvement OUD treatment adherence with long-acting formulations, treatments for opioid craving and withdrawal, treatment of opioid-dependent

pregnant women, prevention and treatment of neonatal opioid withdrawal syndrome, reduction of the lethality of opioid overdose, and prevention of overdose relapse. The National Institute on Drug Abuse (NIDA) has issued a Funding Opportunity Announcement to accelerate the research and development in this area. More information can be found at https://grants.nih.gov/grants/guide/rfa-files/rfa-da-19-002.html. The purpose of this presentation to provide an overview of the advances in the development of new medications and new formulations of approved medications as well as immunotherapies to manage OUD and opioid overdose.

Learning Objective:

1. At the end of the session, participants will gain knowledge about the new medications and new formulations of approved medications that are being studied to prevent and treat Opioid Use Disorders and Opioid Overdose.

Literature Reference:

1. Collins FS, Koroshetz WJ, Volkow ND: Helping to End Addiction Over the Long-term: The Research Plan for the NIH HEAL Initiative. JAMA. 2018 Jul 10;320(2):129-130.

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

METHODOLOGICAL CHALLENGES IN IMPLEMENTING CLINICAL TRIALS TO ADDRESS THE QUESTIONS POSED IN DEVELOPING PERSONALIZED MEDICINE TREATMENTS

Nina Schooler, SUNY Downstate Medical Center

Overall Abstract: The theme of the 2019 meeting is Innovations in Personalized Medicine: from Biomarkers to Patient-Centered Care and this workshop is designed to address some of the methodological challenges involved in developing personalized treatments. There are a number of targets for personalization of treatment. A key one is matching individuals to optimal treatment in order to convert weak treatment effects into strong ones. Historically dating back to the earliest days of our field, the approach focused on phenotypic symptom profiles Modern approaches focus on biomarkers such as brain imaging and genetic profiling and increased precision in assessment of phenotypes that can utilize advanced methods in machine learning and adaptive testing. The challenges include those in trial design, application of appropriate statistical tools, individual assessment strategies that distinguish appropriate patient groups without excessive assessment burden and the application of innovative technologies such as machine learning to integrate large amounts of information. Finally, translating the knowledge gained into appropriate targets for treatment development that can lead to regulatory approval of treatments remains a separate challenge. This workshop is organized under the auspices of the International Society for CNS Clinical Trials and Methodology (ISCTM). ISCTM shares interests, membership and meeting attendance with ASCP but focuses specifically on methodological problems that may impede treatment development and identification of solutions that can speed bringing enhanced treatment options to patients across the range of CNS disorders. Drawing on this expertise and individuals both within and outside the society we propose the following. Jordan Smoller will provide the link between the Keynote session and the workshop specifically drawing upon genomic and imaging biomarkers. Ronald Marcus will consider the use of adaptive methods in design of trials. Isaac Galatzer-Levy will present novel ways in which machine learning can speed the integration of biomarkers into clinical trials. Robert Gibbons will present methods to allow identification of suitable subjects for focused trials that use adaptive computerized testing that tailors assessment to specific patient

groups. Luca Pani will address the important questions of how trials can be translated into medication development that will meet regulatory standards and provide future treatments that are targeted for more specific indications than those presently seen in psychiatry. Because this workshop is linked to the theme of the meeting, we expect strong participation from the audience. Nina Schooler and Stephen Marder, the co-chairs, will facilitate this interaction.

Learning Objectives:

1. Ability to list at least three challenges to design and conduct of clinical trials to develop personalized treatments in psychiatry.
2. Identification of potential methods for addressing challenges.

OPPORTUNITIES FROM GENOMICS FOR ADVANCING PRECISION PSYCHIATRY

Jordan Smoller, Massachusetts General Hospital & Harvard Medical School

Individual Abstract: Though available treatments for psychiatric disorders are effective for many, current practice is largely based on a trial-and-error, one-size-fits-all approach. It is clear that our disorders are etiologically heterogeneous. The availability of clinical features or biomarkers that can parse this heterogeneity and stratify risk could be transformative. A growing catalogue of risk variants and pathways identified through genomic research is providing new targets for therapeutic development. Genetic risk scores derived from these studies offer a new approach to dissecting clinical syndromes and potentially guiding more precise cohort selection for clinical trials. Genomic findings may also enhance the efficiency and success rate of clinical trials by providing experiments of nature that may preview the effects of target modulation relevant to both therapeutic benefits and off-target adverse effects. In addition, genetic and imaging biomarkers may be useful for targeting therapeutic strategies and predicting response in individual patients. This presentation will highlight both proof-of-concept examples of these opportunities and the challenges in implementation. These include examples from other fields (e.g. cardiology) including the use of genetic risk scores for stratifying risk and targeting therapies. The presentation will also describe the particular value of real-world data resources, including electronic health records, for advancing precision psychiatry. This will include recent work from our group using machine learning and genomic risk scores to accelerate genomic studies and identify at risk subgroups in healthcare systems.

Learning Objectives:

1. Describe the utility of genetic findings for validating therapeutic targets and identifying potential off-target effects.
2. Describe the use of genetic risk scores for stratifying patient subgroups with respect to risk and therapeutic response.

Literature References:

1. Smoller JW. The use of electronic health records for psychiatric phenotyping and genomics. Am J Med Genet B Neuropsychiatr Genet. 2017 May 30. doi: 10.1002/ajmg.b.32548. [Epub ahead of print] Review. PMID: 28557243
2. Stein MB, Smoller JW. Precision Psychiatry-Will Genomic Medicine Lead the Way? JAMA Psychiatry. 2018 May 9. doi: 10.1001/jamapsychiatry.2018.0375. [Epub ahead of print] PMID: 29800947

ADVANCES IN CLINICAL CHARACTERIZATION, PREDICTION, AND REMEDIATION THROUGH THE APPLICATION OF MACHINE LEARNING

Isaac Galatzer-Levy, AICure

Individual Abstract: Promising laboratory-based findings often fail to translate to clinical populations, leading to failures to predict and treat psychopathology based on promising biological targets. This failure in translation may be due to foundational differences in how clinical populations are defined where laboratory-based research focuses on direct behavioral, physiological, or neurobiological functioning while clinical research focuses on DSM-based clinical definitions. To bridge this translational gap requires methods to define and predict clinical populations based on basic dimensions of behavior, physiology, and neurobiological dimensions in a manner that is scalable and transportable beyond the laboratory. Such an approach allows for the identification of risk and targets for remediation that can be individualized to the patient's underlying deficit, known as personalized medicine. The speaker will present on new approaches to define and predict clinical functioning and course based on computational methods in machine learning and artificial intelligence that are free from traditional diagnostic mile-markers along with approaches to develop tools and approaches to provide new, data driven, definitions and predictive approaches to health and pathology.

Learning Objectives:

1. To educate the audience on foundational concepts on the use of machine learning and AI for clinical characterization, prediction of risk, and treatment matching in neuropsychiatric conditions.
2. To introduce approaches to characterize and scale neuropsychiatric functioning using technology application.

Literature References:

1. Galatzer-Levy IR, Ruggles KV, Chen Z: Data Science in the Research Domain Criteria Era: Relevance of Machine Learning to the Study of Stress Pathology, Recovery, and Resilience. Chronic Stress 2018; 2:247054701774755
1. 2.MOHRI MEHRYAR: FOUNDATIONS OF MACHINE LEARNING. S.l.: MIT PRESS; 2018.

ROLE OF ADAPTIVE DESIGN METHODOLOGIES IN PRECISION MEDICINE: ADAPTIVE ENRICHMENT DESIGNS BY MODIFYING PRE-SPECIFIED ENROLLMENT CRITERIA

Ronald Marcus, Supernus

Individual Abstract: Randomized trial designs that adaptively change enrollment criteria during a trial, called adaptive enrichment designs, have potential to provide improved information about which subpopulations benefit from new treatments. These designs may be useful when a subpopulation is suspected to be more likely to benefit from the experimental treatment than the rest of the target population. The subpopulation could be defined, for example, by a biomarker, clinical assessments, co-morbidities or risk score measured at baseline. Adaptive enrichment designs have the capability of restricting enrollment to such a subpopulation if early data indicate that the complementary population is not benefiting.

There is interest from the Patient-Centered Outcomes Research Institute in adaptive designs. According to the Patient-Centered Outcomes Research Institute Methodology Report, "adaptive designs are particularly appealing for PCOR (Patient-Centered Outcomes Research) because they could maintain many of the advantages of randomized clinical trials while minimizing some of the disadvantages." Adaptive enrichment designs have potential to improve power for detecting subpopulation treatment effects.

Designs with prespecified rules for modifying the enrollment criteria based on data accrued in an ongoing trial are called adaptive enrichment designs. The US Food and Drug Administration has guidances on adaptive designs for such trials. These guidances generally require that the

populations, enrollment modification rule, and statistical analyses be prespecified in the study protocol. The Enrichment Guidance identifies three strategies for enrichment:
1) Strategies to decrease heterogeneity − to decrease inter-patient variability and intra-patient variability, resulting in increased study power.
2) Prognostic enrichment strategies − choosing patients with a greater likelihood of having a disease-related endpoint event (for event-driven studies) or a substantial worsening in condition (for continuous measurement endpoints).
3) Predictive enrichment strategies − choosing patients more likely to respond to the drug treatment than other patients with the condition being treated, leading to a larger effect size (both absolute and relative) and permit use of a smaller study population. Selection of patients could be based on a specific aspect of a patient's physiology or a disease characteristic that is related in some manner to the study drug's mechanism, or it could be empiric.
The presentation will primarily focus on "Predictive Enrichment Strategies" using adaptive designs in neuroscience clinical trials.

Learning Objectives:

1. Define the three kinds of enrichment designs.
2. Present several examples of Predictive Enrichment Adaptive Design Strategies in neuroscience studies.

Literature References:

1. FDA. Draft Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products.
2. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf
3. Rosenblum M, Hanley D, Adaptive Enrichment Designs for Stroke Clinical Trials. Stroke. 2017; 48:2021-2025.

MEASUREMENT IN PERSONALIZED MEDICINE

Eric Achtyes, Michigan State University College of Human Medicine

Individual Abstract: Measurement is an often overlooked area in mental health research in general and precision medicine in particular. With increasing use of adaptive designs, and the collection of intensive longitudinal data, new approaches to mental health measurement are required. The traditional approach of structured clinical interviews and use of traditional fixed length instruments limits both the quality of measurement and increases the burden of measurement. In this presentation I review new approaches to the measurement of complex traits based on the application of multidimensional item response theory (MIRT) and computerized adaptive testing (CAT). The net result is that we can extract the information from enormous banks of symptom items by adaptive administration of a small number of items that are optimally targeted to the patient's current level of severity. Tailoring items to a patient's severity of illness on each measurement occasion opens the door to high frequency measurement which eliminates response bias produced by repeated administration of the same items to that individual over time. The paradigm shift is from traditional fixed length tests that fix the items and allow measurement precision to vary, to adaptive tests that fix the precision of measurement and allow the items to vary. Using this approach, we can increase the precision of measurement while at the same time decrease the burden of measurement. To help fix ideas, we illustrate the approach using daily assessment of depressive severity over a 6-month period in a patient receiving deep brain stimulation for treatment resistant depression, where personalized changes in the treatment protocol (e.g. stimulation intensity) can be selected on the basis of short-term changes in depressive severity. These measurements are compared and contrasted to traditional clinician ratings that dramatically limit the number of assessments and

introduce inter-rater unreliability. Using these intensive longitudinal measurements, we can then apply new statistical methods (location-scale models) that can identify the selection of an optimal treatment for a subject in terms of both reducing average severity and minimizing within-person variability.

Learning Objectives:

1. Understand statistical approaches to the measurement of complex mental health traits.
2. Understand location-scale models which can identify the effect of treatment(s) on change in both the mean level of severity of illness as well as between and within-person variability.

Literature References:

1. Gibbons RD, Weiss DJ, Pilkonis PA, Frank E, Moore T, Kim JB, Kupfer DJ: Development of a computerized adaptive test for depression. Arch Gen Psychiatry 2012; 69:1104–1112.
2. Sani S, Busnello J, Kochanski R, Cohen Y, Gibbons RD: High frequency measurement of depressive severity in a patient treated for severe treatment resistant depression with deep brain stimulation. Translational Psychiatry 2017;7;e1207.

THE CONTRIBUTION OF REGULATORY SCIENCE TO PERSONALIZED MEDICINE IN PSYCHIATRY

Valentina Mantua, Italian Medicines Agency

Individual Abstract: In theory, the term Precision Medicine defines an approach for the prevention and treatment of diseases that, for each person, takes into account genetic variability, environment and lifestyles. Indeed, the purpose of the 2016 US Precision Medicine Initiative by the National Institutes of Health (NIH) was to study and develop a new patient-centered research model to try to accelerate biomedical discoveries and provide physicians with new tools to identify which treatments work best for the individual person.

In practice, Precision Medicine relates to the unproven assumption that we have entered a new era of medicine in which each individual will receive unique treatment, determined by his/her genome. This widely promulgated notion is mostly likely wrong and, at best, almost impossible to prove and of no practical use in therapeutic products research and development unless effectiveness (i.e. the safety and efficacy profile in real life) and dose titration could be evaluated for each one person at the time and at unsustainable costs. In Psychiatry, the highly variable phenotypic clinical representation when linked to the false impression that treatments should be tailored to the single individual could make most of psychiatric clinical trial virtually impossible.

In this context the delicate role of the regulatory agencies in incentivizing and guiding clinical researchers and pharmaceutical companies moving beyond the model of the so-called blockbuster drugs, could be of ensuring support for the development of solid designs of the N-of-1 trials.

In this regard, one of the challenges lies in being able to identify possible biomarkers that can stratify the patient population according to distinct biological subtypes. This is an undertaking that must certainly involve the patients, but also the regulators globally, the companies, the academic world and the payers. It means recognizing the importance and the limitation that genomic data have in assessing the risks and benefits of a medicine, as well as in providing post-authorization safety and efficacy studies data. In the recent past, the European Medicines Agency (EMA) has not only devoted special attention to research into the use of biomarkers in the development of medicines but has also engaged in the definition of scientific guidelines on pharmacogenomics that encourage the use of genomic data in early diagnosis and the development of personalized treatments albeit with all the considerations discussed above.

Various qualification advices were given on the stratification of instruments and markers to better understand the results of clinical trials. The aim is to verify in advance whether these instruments can ever be accepted and be useful in clinical trials and to support the qualification of innovative development methods in the pharmaceutical sphere because, in the light of the trends that are already becoming established in modern pharmacological research, this would help enhance innovation and help in developing medicines that are truly more effective. The other side of this revolution implies, logically, the exclusion – at least temporarily – from clinical trials of all those who do not possess certain biomarkers, making all diseases, once stratified, from a specific point of view, in some way rare, awaiting a treatment dedicated only to a certain subgroup and eliminating all others. In this context and with similar prospects, the ethical aspects of the new research and the development of "selective" medicines at the molecular level must also be considered with attention.

Learning Objectives:

1. Audience will learn to recognize the critical points in the implications Precision or Personalized Medicine.
2. Audience will learn the regulatory as well as market access and payer issues related to Precision Medicine based clinical trials.

Literature References:

1. Berman Jules J, Precision medicine and the reinvention of human disease, Academic Press, The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom ©2018 Elsevier Inc.
2. https://www.ema.europa.eu/documents/scientific-guideline/concept-paper-predictive-biomarker-based-assay-development-context-drug-development-lifecycle_en.pdf

PSYCHEDELIC DRUG DEVELOPMENT: PERSPECTIVES FROM THE DIVISION OF PSYCHIATRY PRODUCTS, US FOOD AND DRUG ADMINISTRATION*

Javier Muniz, Food and Drug Administration

Overall Abstract: In recent years, there has been a renaissance in clinical research aimed at improving our understanding of the potential therapeutic value of psychedelic drugs (e.g., psilocybin, mescaline, LSD, etc.). Particular focus has been on the treatment of psychiatric conditions, including mood, anxiety, addiction, and trauma-related disorders. Accordingly, the Division has seen an increased number of interactions with sponsors pursuing the research and development of these drugs.

In light of recent advances in the understanding of their potential therapeutic effects, we consider psychedelic drugs to be legitimate candidates for product development. However, there are significant challenges on how to conduct adequate and well-controlled clinical trials to support regulatory approval. Further, the lack of modern regulatory precedent or formal guidance on developing psychedelic drugs for the treatment of psychiatric indications poses regulatory, legal, ethical, and societal challenges for sponsors by virtue of the drugs' unique psychoactive effects.

In this workshop, we will highlight several areas of active dialogue between academia, industry, and regulatory agencies. First, we will summarize the history of psychedelic research, including an overview of landmark studies, with a focus on controlled clinical trials. We will then discuss important considerations regarding the drug product (e.g., development of botanical drug products, nonclinical safety studies, and product quality considerations), as well as potential avenues for special regulatory programs. Next, we will explore issues in clinical trial design, including unique considerations on the assessment of efficacy and safety of

psychedelic drugs. For example, many of these drugs appear to alter neuronal activity far beyond that expected by the pharmacokinetic properties of the drugs. Additional topics that will be discussed in relation to clinical trial design include the role of psychotherapy in psychedelic trials, the importance of set and setting, the impact of patient expectations on study results, and challenges in selecting a treatment comparator and maintaining the adequacy of the blind. Lastly, we will discuss issues related to the legal status of these drugs, including Controlled Substances Staff requirements and challenges in conducting clinical trials with Schedule I substances. We hope that by opening up conversations about these complex issues, we will be able to shed light on how to navigate challenges in the research and development of this class of drugs.

Learning Objectives:

1. Participants will be familiar with ongoing clinical trial design challenges in the development of psychedelic drugs.
2. Participants will be familiar with unique considerations on the assessment of efficacy and safety of psychedelic drugs.

BRIDGING THE PAST, PRESENT, AND FUTURE OF PSYCHEDELIC DRUG RESEARCH AND DEVELOPMENT

Sean Belouin, United States Public Health Service

Individual Abstract: This presentation provides a brief historical perspective of psychedelic drug research and development over the last 50 years, and the current reemergence of clinical research using psychedelics as potential breakthrough therapies for psychiatric disorders refractory to current evidence-based treatments. Given the deepening resurgence of interest in psychedelic research, there needs to be significantly expanded understanding of the mechanisms-of-action(s) for psychedelic drugs that can better explain their potential clinical effects on brain-related diseases and disorders. Moreover, past landmark studies during the 1960s and 70s conducted with psychedelics for certain psychiatric conditions proved insufficient from a safety and efficacy perspective because of inadequate trial designs. There is evidence that constraining regulatory controls imposed during the late 1960s and early 70s contributed to stalled research in this field. In the late 1990s, renewed interest emerged with expanding research nationally and internationally. In 2018, psilocybin received a breakthrough therapy designation for the treatment resistant depression. Given current advances in understanding the potential therapeutic effects of psychedelic drugs as legitimate candidates for product development, there is an acknowledged need to engage in open dialogue with sponsors, funders, and the public. As part of any current decision-making process, it is crucial to understand what occurred in the past, so sponsors may be guided appropriately going forward to satisfy those regulatory requirements needed for drug product approval.

Learning Objectives:

1. Participants will be able to discuss the results and limitations of historical landmark studies on use of psychedelics for treatment of certain psychiatric conditions.
2. Participants will be able to identify at least two methodological challenges to clinical research of psychedelics.

Literature References:

1. Belouin, S.J., Henningfield, J.E., 2018. Psychedelics: where we are now, why we got here, what we must do. Neuropharmacology. https://doi.org/10.1016/j.neuropharm. 2018.02.018 pii: S0028-3908(18)30075-3, [Epub ahead of print].

2. Calderon, S.N., Hunt, J., Klein, M., 2017. A regulatory perspective on the evaluation of hallucinogen drugs for human use. Neuropharmacology. https://doi.org/10.1016/j.neuropharm.2017.11.028 pii: S0028-3908(17)30537-3, [Epub ahead of print].

CHALLENGES IN CONDUCTING CLINICAL RESEARCH WITH SCHEDULE I HALLUCINOGENS

Katherine Bonson, Food and Drug Administration

Individual Abstract: Clinical research with hallucinogens began in the United States in 1949. Throughout the 1950s and 1960s, hallucinogens such as lysergic acid diethylamide (LSD) were investigated for a variety of psychiatric indications, including: as an aid in treatment of schizophrenia; as a means of creating a "model psychosis"; as a direct antidepressant; and as an adjunct to psychotherapy. Research with all drugs, including LSD, have always been conducted under federal regulatory controls, including the 1938 Food Drug and Cosmetic Act (FDCA; which ensured the safety of drugs) and the 1962 Kefauver-Harris Amendments to the FDCA (which described appropriate scientific methodology and ensured drug efficacy). However, the requirements of the 1962 Amendments were not immediately adopted by most clinical sites in the way we understand them now because at that time, even FDA was internally debating how the regulations should be implemented. Eventually, these regulations critically improved scientific standards and subject protections, which led to the curtailment of many unethical research practices common at that time for clinical research with any class of drugs. The decline in LSD research in the U.S. by the 1970s can be attributed in large part to the introduction of controls on legal access to hallucinogens through both the 1962 Amendments, as well as the subsequent Controlled Substances Act (CSA) of 1970. This presentation will detail how human studies conducted with LSD in the 1960s and 1970s struggled to fulfill regulatory requirements and produced investigations that are often best understood as proof-of-concept studies.

The current resurgence of investigations with hallucinogens occurs in the wake of this history and includes both small-scale pilot studies and larger-scale drug development studies. What is different now is that all researchers (whether in academic or industry settings) who conduct these studies must fully comply with FDA and DEA regulations. Among these regulations are those that require that a drug that with central nervous system activity be evaluated for abuse potential. This assessment is carried out by the Controlled Substance Staff at FDA, based on the principles laid out in the 2017 Guidance for Industry: Assessment of the Abuse Potential of Drugs. This presentation will detail which abuse-related studies are required for hallucinogens, including evaluations of chemistry, receptor binding, animal behavior, human adverse events and (if there are abuse-related signals in the other studies) the need for a human abuse potential study. These abuse-related studies inform how Section 9 (Drug Abuse and Dependence) of the drug label will be written and determine the recommendation for scheduling placement under the CSA, if the NDA for that drug is approved based on its safety and efficacy.

Learning Objectives:

Following the presentation, participants will be able to:

1. Understand how clinical research with hallucinogens in the 1960s and 1970s was impacted by the 1962 Amendments to the Food Drug and Cosmetic Act and the 1970 Controlled Substances Act in terms of clinical study design and access to study drugs.
2. Discuss how FDA evaluates the abuse potential of Schedule I substances that are under investigation to become drug products.

Literature References:

1. Bonson, KR (2018) Regulation of human research with LSD in the United States (1949-1987) Psychopharmacology 235(2):591-604.
2. FDA Guidance for Industry: Assessment of the Abuse Potential of Drugs (2017).

THE PATH TO PSYCHEDELIC DRUG PRODUCT DEVELOPMENT

Nancy Dickinson, FDA

Individual Abstract: Ensuring a quality psychedelic drug product for use in clinical trials requires navigating the applicable regulations and guidance. This presentation will provide an overview of drug substance considerations, such as origin of the psychedelic drug, dosing regimen, and the amount of previous human exposure, that determine a psychedelic drug's development program.

For hundreds of years, humans have used naturally occurring psychedelics (e.g., psilocybin, dimethyltryptamine, and mescaline) in healing and religious rituals. From a regulatory perspective, these drugs fall into two distinct categories, each with their own set of guidance recommendations: botanicals or nonbotanicals. The FDA advice to prepare the botanical or nonbotanical psychedelics for use in clinical trials is different due to the amount of past human experience, complex mixtures with lack of a distinct active ingredient, or use of a synthesized small molecule. Terminology surrounding botanicals, nonbotanical drugs, small molecules, drug substance, and drug product will be defined in this presentation.

Psychedelic drugs may also present a different dosing paradigm than traditional psychiatric drugs taken chronically; this has implications on requirements for nonclinical and product quality characterization. For example, a psychedelic drug, theoretically, may be recommended for use one time or for a small number of doses. The amount of expected human exposure with a psychedelic will affect the type and amount of nonclinical animal research necessary for safety. This presentation will explain the nuances of incorporating historical human use information into drug development, in lieu of repeating nonclinical research, when applicable.

When potential botanical or nonbotanical drug substances are used for clinical research, they must meet certain safety-related manufacturing specifications prior to ingestion. These standards include manufacturing controls, which become more stringent as the phase of drug development progresses. The gap between novel molecule or botanical compound to psychedelic drug product prepared for clinical trials is attainable.

These issues will be of potential interest to sponsors and investigators who are developing psychedelic drug products for marketing approval for psychiatric diseases.

Learning Objectives:

1. Participants will be able to describe which factors of a psychedelic substance guide the drug's Phase 1 development program.
2. Participants will be able to describe the differences between botanical and nonbotanical drug product development.

Literature References:

1. Food and Drug Administration. (2016.) Botanical Drug Development Guidance for Industry.
   Retrieved from https://www.fda.gov/downloads/Drugs/Guidances/UCM458484.pdf
2. Food and Drug Administration. (2010.) Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.
   Retrieved from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf

CLINICAL TRIAL DESIGN: ESTABLISHING SAFETY AND EFFECTIVENESS IN PSYCHEDELIC DRUG DEVELOPMENT

Bernard Fischer, U.S. Food and Drug Administration

Individual Abstract: Psychedelic drugs may have important therapeutic effects on CNS disorders such as anxiety, depression, posttraumatic stress disorder, and substance use disorder. It is unknown whether the psychedelic properties of these drugs are a by-product of their mechanism of action or if their psychedelic properties are necessary for the observed therapeutic effect. Regardless, these drugs present unique challenges in clinical trial design. Safety challenges include the concurrent use of antidepressants (most known psychedelic drugs act on the serotonergic system), the possibility of a "bad trip" (e.g., anxiety, a feeling of entrapment, or a loss of a sense of self-identity), and "flashbacks" (hallucinogen persisting perception disorder: a recurrence of psychedelic drug effect occurring days to weeks after drug use). Efficacy challenges include timing for endpoint measures, establishing the duration of effect, and (in combination with safety considerations) dosing. In contrast with a typical psychiatric drug, improvement of symptoms may continue after the drug is discontinued. Based on what we know of psychedelic drugs, it appears daily use would not only be impractical, but unnecessary—however, a label would need to include information on the need for an additional course of drug during the current illness episode or the patient's lifetime. The establishment of an optimum dose should consider a "psycholytic" approach (more frequent, lower doses) or a "psychedelic" approach (higher doses triggering a "mystical" experience). This talk will review current regulatory thinking in addressing these challenges.

Learning Objectives:

1. Participants will be able to describe unique safety and efficacy concerns in the use of psychedelic drugs.
2. Participants will be able to describe current regulatory thinking on trial design for psychedelic drugs.

Literature References:

1. Kyzar EJ, Nichols CD, Gainetdinov RR, Nichols DE, Kalueff AV. Psychedelic drugs in biomedicine. Trends Pharmacol Sci 2017; 38(11):992-1005
2. Johnson MW, Richards WA, Griffiths, RR. Human hallucinogen research: Guidelines for safety. J Psychopharmacol 2008; 22(6):603-20.

REGULATORY PERSPECTIVES ON PSYCHOTHERAPY IN PSYCHEDELIC DRUG DEVELOPMENT

Michael Davis, US Food and Drug Administration

Individual Abstract: Although proposed therapeutic doses of psychedelics such as psilocybin and LSD are thought to have a relatively low liability for physiological adverse reactions, psychedelics have the potential to cause significant psychological adverse reactions, including acute anxiety, dysphoria, and/or paranoia. Integration of psychotherapy with psychedelic drug administration developed, in part, following early studies which reported a decreased incidence of psychological adverse reactions, as well as an increased incidence of positive experiences, when investigators made efforts to optimize the set (psychological state) and setting (environment) for study subjects. In addition, investigators have proposed that the effectiveness of psychotherapy can be augmented or that its processes can be accelerated by psychedelics. Specifically, researchers hypothesize that psychedelics may produce a state of mind that facilitates access to new associative pathways for salient emotions and memories, enabling learning of new cognitive, emotional, and behavioral responses.

Psychotherapy has thus been an integral component of psychedelic treatment studies for over 50 years. Although the forms of psychotherapy have differed, many, if not most current psychedelic researchers believe that psychological preparation prior to treatment, support during the drug's acute effect period, and some form of post-session integration are important mediators of both safety and efficacy for psychedelic treatments. The proposed link between psychotherapy and psychedelic drug administration differs from that of most currently marketed psychiatric medications. Although the Prescribing Information for a small number of FDA-approved drugs includes general language related to psychotherapy in Indications and Usage, Dosage and Administration, and/or Clinical Studies sections, most psychiatric medications were developed and labeled for use without regard to concomitant psychotherapy. Furthermore, the FDA does not regulate the practice of psychotherapy.

Thus, the role of psychotherapy in psychedelic drug development raises several regulatory considerations. Specific issues that will be discussed in this presentation include:

1. What are the most basic characteristics of psychological support that should be implemented in psychedelic treatment studies to protect the safety of study subjects?
2. If psychotherapy (beyond psychological support during the acute drug experience) is a critical mediator of efficacy for a psychedelic treatment, does this need to be demonstrated? How important is it to establish whether the same benefits could be achieved without adjunctive psychotherapy, or whether psychotherapy alone has an equal or superior benefit/risk profile compared to psychedelic-adjunctive psychotherapy?
3. If adjunctive psychotherapy is critical for safe and effective psychedelic treatment, in how much detail should this be presented in product labeling?

Learning Objectives:

1. Participants will be able to describe basic methods that should be implemented in psychedelic trials to minimize the risk of significant psychological adverse reactions.
2. Participants will be able to describe at least two regulatory issues related to the role of psychotherapy in psychedelic drug development.

Literature References:

1. Carhart-Harris R, Leech R, Williams T, Erritzoe D, Abbasi N, Bargiotas T, Hobden P, Sharp D, Evans J, Feilding A, Wise R, Nutt D: Implications for psychedelic-assisted psychotherapy: functional magnetic resonance imaging study with psilocybin. British Journal of Psychiatry 2012; 200:238-244.
2. Schenberg E: Psychedelic-Assisted Psychotherapy: A Paradigm Shift in Psychiatric Research and Development. Frontiers in Pharmacology 2018; 9:733.

PLACEBO RESPONSE: CHALLENGES IN MAINTAINING THE BLIND IN PSYCHEDELIC CLINICAL TRIALS.

Javier Muniz, Food and Drug Administration

Individual Abstract: There is no denying that placebo response is real and important in psychiatric drug development. The magnitude of placebo response in psychiatric clinical trials has markedly increased over the past 20 years, posing challenges in demonstrating the effectiveness of treatments with mild-to-moderate effect sizes. Research into the placebo response has identified several contributing factors, including therapeutic alliance with the provider, expectations of treatment efficacy, and conditioned response. Furthermore, the mode of treatment delivery can influence these factors.

Elements that are particularly salient in psychedelic research (e.g., "set and setting", unblinding due to drug effects, subject expectations, psychotherapeutic interventions, etc.) have impact on treatment response which is not entirely understood and could present unique challenges in the

interpretation of the observed results. Nonetheless, randomized, placebo-controlled trials remain the current standard for gaining regulatory approval.
To maintain the adequacy of the blind, researchers have adopted diverse strategies in their clinical trial design armamentarium (e.g., use of other psychoactive drugs with no known therapeutic effects as comparators, subthreshold dosing, incorporation of various drug doses as treatment arms, etc.). To help guide future drug development in this therapeutic class, this presentation will focus on the Division's current thinking on the advantages and disadvantages of commonly used strategies as well as potentially innovative ideas on maintaining the integrity of the blind.

Learning Objectives:

1. Participants will be able to identify at least two factors contributing to the placebo response.
2. Participants will be able to evaluate strategies proposed by psychedelic researchers to maintain the adequacy of the blind during clinical trials.

Literature References:

1. Rucker JJH, Iliff J, Nutt DJ. Psychiatry & the psychedelic drugs. Past, present & future. Neuropharmacology. 2017 Dec 25.
2. Ballou S, Beath A, Kaptchuk TJ, Hirsch W, Sommers T, Nee J, Iturrino J, Rangan, V, Singh P, Jones M, Lembo A. Factors Associated With Response to Placebo in Patients With Irritable Bowel Syndrome and Constipation. Clin Gastroenterol Hepatol. 2018 Nov 6.

TMS, KETAMINE OR ECT: 3 CASE PRESENTATIONS

Michael Henry, Massachusetts General Hospital

Overall Abstract: Treatment resistant depression (TRD) afflicts up to 20% of patients diagnosed with major depression (MDD). The emergence of transcranial magnetic stimulation (TMS) and ketamine as effective antidepressant therapies has opened up new treatment options for these patients. However, their place in the treatment algorithm has not been well defined, and little is known about their comparative efficacy to electroconvulsive therapy (ECT) which has long been considered the gold standard. The purpose of this workshop is to discuss current approaches and highlight the need for comparative data regarding the efficacy of each treatment. Strong audience participation is expected for the case discussions.

Learning Objectives:

1. Participants will understand the varying degrees of treatment resistance encountered clinically in TRD.
2. Participants will understand the gaps in the current evidence available to guide the use of TMS, ECT, and Ketamine in treatment resistant depression.

DEFINITION AND PREVALENCE OF TREATMENT RESISTANCE IN DEPRESSION

Maurizio Fava, Massachusetts General Hospital

Individual Abstract: Almost half of depressed patients do not respond to their first antidepressant treatment of adequate dose and duration. When patients who have not responded to a first trial go on to subsequent trials of antidepressant monotherapy, the benefits tend to be extremely modest and this is why there has been a proliferation of pharmacological augmentation strategies for the treatment of resistant depression. Many of these strategies do not have empirical evidence and are often based on anecdotal impressions. On the other hand,

fairly robust evidence is available for the use of atypical antipsychotics such as quetiapine, aripiprazole, and brexpiprazole. The actual prevalence of treatment-resistant depression derived from efficacy trials is likely to be an underestimate of the actual occurrence of the phenomenon, as adherence to treatment tends to be poorer in real-world settings. It is critical to standardize the assessment of treatment resistance and a number of instruments such as the Antidepressant Treatment Response Questionnaire (ATRQ) are used both in practice and in clinical trials for this purpose. Treatment-resistant depression (TRD) patients can be defined as those who fail to respond to standard doses of antidepressants administered continuously for at least 6 to 8 weeks. Additional requirements of this operational definition are an accurate diagnosis of depressive disorder, and patient adherence to treatment. Despite the existing pharmacological tools, TRD remains a clinical challenge for practitioners and, for that reason, clinicians are faced with the dilemma of choosing among three major next steps: TMS, Ketamine, or ECT. This workshop will focus on these strategies.

Learning Objectives:

1. To become familiar with the definition of treatment resistance in depression.
2. To learn about the standard assessments of treatment resistance in depression.

Literature References:

1. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am. 1996 Jun;19(2):179-200.
2. Nierenberg AA, Katz J, Fava M. A critical overview of the pharmacologic management of treatment-resistant depression. Psychiatr Clin North Am. 2007 Mar;30(1):13-29.

TREATMENT SELECTION IN TRANSCRANIAL MAGNETIC STIMULATION (TMS): A CASE-BASED DISCUSSION

Joan Camprodon, Massachusetts General Hospital, Harvard Medical School

Individual Abstract: Transcranial Magnetic Stimulation (TMS) is a noninvasive neuromodulation technique with diagnostic and therapeutic clinical applications, including FDA-clearance for the treatment of treatment resistant major depressive disorder (TR-MDD), obsessive compulsive disorder and migraines. In the context of other well-established (ECT) and novel (Ketamine) treatment options for TE-MDD, we will present a clinical case to frame a discussion and debate regarding therapeutic algorithms and treatment selection (e.g. TMS vs. ECT vs. Ketamine) with an emphasis on dimensional and circuit-focused clinical formulations, the availability of clinical and biomarker predictors of response and individualization of treatment parameters.

Learning Objectives:

1. To understand the clinical algorithms guiding treatment selection for TMS.
2. To understand current practices for individualization of TMS therapy.

Literature References:

1. Camprodon JA, Pascual-Leone A. Beyond therapeutics: multimodal TMS applications for circuit-based psychiatry. JAMA Psychiatry. 2016 Apr 1;73(4):407-8.
2. Camprodon JA. Transcranial Magnetic Stimulation. In: Camprodon JA, Rauch SL, Greenberg BD, Dougherty DD (eds.). Psychiatric Neurotherapeutics: Contemporary Surgical & Device-Based Treatments in Psychiatry. New York, NY: Humana Press. 2016.

KETAMINE FOR TREATMENT-RESISTANT DEPRESSION: SYMPTOM IMPROVEMENT VS. FUNCTIONAL RECOVERY IN CLINICAL SETTING

Cristina Cusin, Massachusetts General Hospital

Individual Abstract: Ketamine represent the first novel rapid treatment available for patients who have failed standard antidepressants. A ketamine clinic presents challenges similar to those encountered in ECT and TMS services, and other challenges that are significantly different, such as how to manage the risk of addiction. We will review some of the most common issues encountered in a ketamine clinic, with focus on the difficulties in evaluating patients, administering and managing intranasal ketamine, the risk for suicidal behaviors and the coordination with other forms of interventions.

We will discuss the results from two clinics, one affiliated with an academic medical center and one in private practice, in terms of patient population, response rate and retention.

For patients with longstanding treatment-refractory depression the severity of illness often caused a marked functional decline. We will discuss the preliminary results of our pilot study of combining IN ketamine with CBT intervention developed for patients with partial improvement targeting functional recovery. Finally, we will discuss a future ketamine clinic model closer to rehabilitation for chronic medical diseases and how the goals of treatment should be modified in this population.

Learning Objectives:

1. Review indications and contraindications for ketamine treatment.
2. Learn common challenges in managing patients on long-term ketamine treatment.

Literature References:

1. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. Sanacora G, Frye MA, McDonald W, et al. American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments. JAMA Psychiatry. 2017 Apr 1;74(4):399-405.
2. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2018 Feb 1;75(2):139-148

PROLONGED SEVERE DEPRESSION IN A 70 YO WITH BIPOLAR DISORDER: ECT?

Michael Henry, Massachusetts General Hospital

Individual Abstract: Electroconvulsive Therapy (ECT) has long been thought of as the gold standard for treatment resistant depression, either bipolar or unipolar. Today, that is challenged by transcranial magnetic stimulation and ketamine. The case that will be presented for discussion is of a 70-year-old man with Bipolar I disorder who has suffered through a 2 year long episode of depression. The question for the audience's consideration is which of the 3 treatments should be chosen first and why. The session will conclude with a review of the efficacy data for ECT in depression with an emphasis on bipolar depression.

Learning Objectives:

1. Understand treatment options for medication resistant bipolar depression.
2. Review the available evidence for the use of TMS, Ketamine, and ECT in Bipolar Depression.

Literature References:

1. 1. Dierckx B, Heijnen WT, Broek WW, Birkenhäger TK. Efficacy of electroconvulsive therapy in bipolar versus unipolar major depression: a meta-analysis. Bipolar Disorders, 2012, 14,146-150.

2. Perugia G, Medda P, Tonib C, Mariania MG, Soccia C, Mauria M. The Role of Electroconvulsive Therapy (ECT) in Bipolar Disorder: Effectiveness in 522 Patients with Bipolar Depression, Mixed-state, Mania and Catatonic Features. Current Neuropharmacology, 2017, 15, 359-371

Friday, May 31, 2019

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

CNS CLINICAL TRIALS IN CHINA: ACHIEVEMENTS, CHALLENGES, AND OPPORTUNITIES*

Jianping Zhang, The Zucker Hillside Hospital

Overall Abstract: Psychopharmacology research has grown rapidly in China in the past two decades. Due to the large population, there is an unmet demand in mental health services and pharmacotherapy. The Chinese government has invested tremendously to improve the psychiatric services including standardized research platforms. International collaborations with Chinese researchers have resulted in high impact findings in the field. CNS clinical trials have participating sites in China and have recruited many patients. There are advantages of conducting CNS trials in China, such as being able to recruit large samples, patients being relatively uncontaminated by drug abuse, and existence of multi-site collaboration platform. Challenges and concerns also exist including data quality issues in CNS trials. This symposium aims to describe the current state of psychopharmacology research in China, identify challenging issues in the field, and seek opportunities for future collaboration with international researchers.

There will be four speakers on the panel. Dr. Huafang Li from Shanghai Mental Health Center will discuss multi-center CNS clinical trial operation and new drug development in China. Dr. Weihua Yue from Peking University Institute of Mental Health will discuss recent pharmacogenomics research, particularly genomic biomarkers of antipsychotic drug response. Dr. Jijun Wang from Shanghai Mental Health Center will discuss using neuroimaging biomarkers to predict treatment response in first episode psychosis. Dr. Jingping Zhao from the Institute of Mental Health at the Second Xiangya Hospital will discuss recent antipsychotic clinical trials conducted in China. Dr. Donald Goff from New York University Langone Medical Center will serve as the discussant for the symposium.

Learning Objectives:

1. Identify challenges and opportunities of CNS clinical trials and psychopharmacology research in China.
2. Incorporate biomarkers including genomic and neuroimaging markers in clinical trials and drug development.

AN IMPROVEMENT PLAN TO PROMOTE CHINA'S CLINICAL RESEARCH IN PSYCHIATRY

Yifeng Shen, Shanghai Mental Health Center

Individual Abstract: Benefiting from the funding of the China National Science and Technology Major Project on “Significant New Drug Creation” from 2008-2020, our team obtains a valuable opportunity to rapidly develop in clinical research. However, comparing with strong growth momentum in pharmaceutical R&D, driven by the reform in drug

evaluation and review policies, development of clinical research in psychiatry lags behind other parts of the drug innovation. We will share with you our opinions as following to promote clinical research in this field.

1) Emerging technologies are promoting innovations in clinical research.

Emerging concepts and technologies such as precision medicine and electronic rating scales with centralized evaluation are giving birth to a series of innovative treatments for major depressive disorder, especially on cognitive function; the increasing availability of healthcare big data can potentially transform the way we traditionally conduct clinical research and trials; the development of tele-medicine and artificial intelligence can disrupt how doctors interact with patients in the traditional experience-based clinical settings. However, none of these technological trends can bypass clinical research. As emerging technological trends constantly drive innovations of clinical research, China's clinical research needs to leverage these trends and become the leader in such innovation.

The follow-up development of psychiatry research in China will pay more attention to the planning strategy of research and development (R&D) of new drugs; the use of early pharmacokinetics/pharmacodynamics models; the model-based design and decision; the discovery of specific biomarkers; the establishment of key indicators of patients report outcomes; as well as electronic data capture–based entire process real-time quality control, to reach the goal of enhancing the quality, efficiency, and accuracy of research.

2) Underlying challenges in trial design and execution lie in the mindset, capabilities and management mechanisms of all stakeholders.

Underlying challenges faced by all stakeholders, including sponsors, hospitals, GCP sites, investigator teams, and 3rd-party providers. The sponsors need to improve both mindset and capability, i.e., shifting perception about their own responsibilities and mindset to work together with the investigators, improving design capability for the trial plans and clinical research management system.

In the context of fast-growing clinical demand, 3rd-party providers are faced with several main challenges: high turnover rate of employees, large capability gaps and lack of industry-wide norms and standards.

3) Starting up a top-down design at the national level.

Reform rating and performance evaluation criteria for hospitals and departments; reform professional title appraisal and performance evaluation process for doctors; include clinical research related indicators into the evaluation process and increase the weighted importance of these indicators; structure and evaluate clinical research staff separately from clinical staff and allocate separate bed quota for research to ensure sufficient, dedicated research resources.

Strengthen the holistic supporting mechanisms for clinical research, including talent development and training, clinical trial subject education and protection, as well as establishing a collaborative review model of IRBs to participate in breakthroughs in psychotropic drug development.

Learning Objectives:

1. To learn what is most feasible solution to promote China's clinical research in psychiatry.
2. To learn What are important factors to support investigator initiate study in China.

Literature References:

1. Shen Y, Li H: General Information on Clinical Psychopharmacology in China. J Clin Psychopharmacol. 2018; 38:107-110
2. Li HF, Gu NF: History of clinical psychopharmacology in China. Chin J New Drugs Clin Remedies. 2011; 30:881–885

PHARMACOGENOMIC STUDY OF ANTIPSYCHOTIC MEDICINES IN CHINESE HAN POPULATION

Weihua Yue, Peking University Sixth Hospital

Individual Abstract: In the present study, we did a two-stage pharmacogenomic genome-wide association study of treatment response or antipsychotic-induced weight gain (AIWG) in patients with schizophrenia. The patients randomly assigned to aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, haloperidol, and perphenazine. The sample size of this study (n=2413 in the discovery cohort and 1379 in the replication samples) is one of the largest reported so far. We have detected five novel significant loci (MEGF10, SLC1A1, PCDH7, CNTNAP5, and TNIK) associated with general treatment response (ie, combining all antipsychotics). We calculated the genetic risk score on the basis of five significant SNPs, the discriminative power to distinguish responders from non-responders remained moderate (best area under the curve 71.3%).

For the AIWG, the two-stage GWAS identified two genome-wide significant SNPs with AIWG at two genes: the PTPRD gene (protein tyrosine phosphatase, receptor type D; rs10978083, P=4.34×10-12) and PEPD gene (peptidase D; rs731839, P=5.50×10-10), respectively. Furthermore, the polygenic risk score calculated based on the two SNPs (rs10978083 and rs731839) could significantly predict AIWG in the discovery (P=1.47×10-12) and follow-up cohort (P=1.39×10–2).

We have identified genes related to synaptic function, neurotransmitter receptors, and schizophrenia risk that are associated with response to antipsychotics. We have also identified genes related to metabolic process that are associated with AIWG. These findings improve understanding of the mechanisms underlying treatment responses, and the identified biomarkers could eventually guide choice of antipsychotic in patients with schizophrenia.

Learning Objectives:

1. To learn genomic predictors of antipsychotic drug response in schizophrenia.
2. To learn to use pharmacogenomic biomarkers in clinical practice.

Literature References:

1. Zhang JP, Malhotra AK. Pharmacogenetics and antipsychotics: therapeutic efficacy and side effects prediction. Exper Opin Drug Metabol Toxicol 2011; 7: 9–37.
2. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature 2014; 511: 421–27.

ASSOCIATION OF HIPPOCAMPAL ATROPHY WITH DURATION OF UNTREATED PSYCHOSIS AND MOLECULAR BIOMARKERS DURING INITIAL ANTIPSYCHOTIC TREATMENT OF FIRST-EPISODE PSYCHOSIS

Hao Hu, Shanghai Mental Health Center

Individual Abstract: Objective: Duration of untreated psychosis (DUP) has been associated with poor outcome in schizophrenia, but the mechanism is not known. To determine whether hippocampal volume loss occurs during the initial antipsychotic treatment and whether it is related to DUP. An exploratory objective was to examine molecular biomarkers in relation to hippocampal volume loss and DUP.

Methods: A naturalistic longitudinal study with matched healthy controls was conducted at Shanghai Mental Health Center. Between March 5, 2013, and October 8, 2014. 71 medication-naive individuals with nonaffective first-episode psychosis (FEP) and 73 age- and sex-matched healthy controls were recruited. After approximately 8 weeks, 31 participants with FEP and 32 controls were reassessed. Associations of left hippocampal volumetric integrity (LHVI) with

DUP, 13 peripheral molecular biomarkers and 14 single-nucleotide polymorphisms (SNPs) from 12 candidate genes were analyzed.
Results: The full sample consisted of 71 individuals with FEP (39women and 32 men; mean [SD] age, 25.2 [7.7] years) and 73 healthy controls (40 women and 33 men; mean [SD] age, 23.9 [6.4] years). Baseline median left HVI was lower in the FEP group (n = 57) compared with the controls (n = 54) (0.9275 vs 0.9512; difference in point estimate, −0.020 [95% CI, −0.029 to −0.010]; P = .001). During approximately 8 weeks of antipsychotic treatment, left HVI decreased in 24 participants with FEP at a median annualized rate of −.03791 (–4.1% annualized change from baseline) compared with an increase of 0.00115 (0.13% annualized change from baseline) in 31 controls (difference in point estimate, −0.0424 [95% CI, −0.0707 to −0.0164]; P = .001). The change in left HVI was inversely associated with DUP (r = −0.61; P = .002). Similar results were found for right HVI, although the association between change in right HVI and DUP did not achieve statistical significance (r = −0.35; P = .10). Exploratory analyses restricted to the left HVI revealed an association between left HVI and markers of inflammation, oxidative stress, brain-derived neurotrophic factor, glial injury, and markers reflecting dopaminergic and glutamatergic transmission.
Conclusions: An association between longer DUP and accelerated hippocampal atrophy during initial treatment suggests that psychosis may have persistent, possibly deleterious, effects on brain structure. Additional studies are needed to replicate these exploratory findings of molecular mechanisms by which untreated psychosis may affect hippocampal volume and to determine whether these effects account for the known association between longer DUP and poor outcome.

Learning Objectives:

1. To learn the neuroimaging biomarkers of poor antipsychotic drug response associated with long DUP.
2. To learn strategies of predicting antipsychotic drug response in first episode psychosis.

Literature References:

1. Addington J, Heinssen RK, Robinson DG, Schooler NR, Marcy P, Brunette MF, Correll CU, Estroff S, Mueser KT, Penn D, Robinson JA, Rosenheck RA, Azrin ST, Goldstein AB, Severe J, Kane JM. Duration of Untreated Psychosis in Community Treatment Settings in the United States. Psychiatric services. 2015;66:753-756.
2. Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. Am J Psychiatry. 2005;162:1785-1804.

MINOCYCLINE ADJUNCTIVE TREATMENT TO RISPERIDONE FOR NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: ASSOCIATION WITH PRO-INFLAMMATORY CYTOKINE LEVELS

Jingping Zhao, Second Xiangya Hospital, Central South University

Individual Abstract: Background: We attempted to replicate the efficacy of minocycline, a second-generation tetracycline, as adjunctive therapy for the negative symptoms of schizophrenia, and to investigate its association with pro-inflammatory cytokine levels.
Methods: Seventy-five schizophrenia patients with negative symptoms entered a 3-month, double blind, randomized, placebo-controlled clinical trial. Subjects were assigned low dose (100mg per day) or high dose minocycline (200mg per day) or placebo combined with risperidone. The outcomes used the Scale for the Assessment of Negative Symptoms (SANS) and the Positive and Negative Syndrome Scale (PANSS)-negative subscale. We assessed three pro-inflammatory cytokines in serum: interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor–α (TNF-α).

Results: Subjects receiving high dose minocycline not only had greater improvements on the SANS total scores and PANSS negative subscale scores ($P < 0.01$), but also had greater reductions in IL-1β and IL-6 serum levels ($P < 0.01$) when compared with those receiving low dose minocycline or placebo. The improvement in negative symptoms with minocycline was significantly correlated with the reduction of IL-1β and IL-6 serum levels ($P < 0.05$).
Conclusions: Schizophrenia patients showed a significant improvement in negative symptoms with the addition of minocycline to risperidone. Reducing pro-inflammatory cytokines may play an important role in the potential mechanism for efficacy.

Learning Objectives:

1. To learn strategies of treating negative symptoms of schizophrenia.
2. To learn the efficacy of minocycline in augmenting treatment of risperidone for negative symptoms.

Literature References:

1. Elizabeth H, Kristin H, Daniel W, Christian, K, 2010. Assessment of pharmacotherapy for negative symptoms of schizophrenia. Curr Psychiatry Rep. 12, 563-571
2. Chaudhry IB, Hallak J, Husain N, Minhas F, Stirling J, Richardson P, et al., 2012. Minocycline benefits negative symptoms in early schizophrenia: a randomized double-blind placebo-controlled clinical trial in patients on standard treatment. J Psychopharmacol. 26, 1185-1193.

REPURPOSING DRUGS FOR SCHIZOPHRENIA: INSIGHTS FROM IMMUNE AND RENIN-ANGIOTENSIN SYSTEMS*

Antonio Teixeira, University of Texas Health Science Center at Houston

Overall Abstract: The mainstay of pharmacological treatment of schizophrenia relies on anti-dopaminergic drugs. While they can improve psychotic symptoms, they lack efficacy on negative and cognitive dimensions of the illness. Besides, these drugs are associated with multiple motor and metabolic effects, and a significant number of patients do not respond well to them. Taken into account these facts and the complexity of the physiopathology of schizophrenia, it is worth evaluating other mechanisms or pathways as potential therapeutic targets. The repurposing of drugs with established safety and pharmacodynamic profiles is an interesting strategy in this context.
In this panel, Dr. Teixeira will discuss the role played by immune mechanisms in schizophrenia, and the available clinical evidence on anti-inflammatory strategies against the illness. Besides being associated with neuroinflammatory responses, the renin-angiotensin system has been implicated in glutamate dysfunction. Dr. Pessoa Rocha will discuss pre-clinical and clinical evidence on the role of angiotensin II type 1 (AT1) receptor blockers in schizophrenia. Dr. Macedo will discuss pre-clinical evidence on indoleamine 2,3-dioxygenase (IDO) inhibitors, that have been evaluated as an immunomodulatory strategy for cancer treatment, in animal models of schizophrenia. Dr. Salgado will be the discussant.

Learning Objectives:

1. Describe the immune changes and the effects of immune-based strategies in schizophrenia.
2. Identify the therapeutic possibilities when addressing the renin-angiotensin system.

IMMUNE DYSFUNCTION AS A TARGET FOR THERAPEUTIC INTERVENTION IN SCHIZOPHRENIA

Antonio Teixeira, University of Texas Health Science Center at Houston

Individual Abstract: Background: Schizophrenia and inflammation are closely intertwined, and possibly powering each other in a bidirectional loop. Inflammation may contribute to schizophrenia pathophysiology and clinical symptoms, more specifically, cognitive performance.

Methods: Patients with chronic stable schizophrenia and healthy controls underwent clinical and cognitive evaluation (BACS and SCoRS), and assessment of blood levels of cytokines and cannabinoid receptor expression on the surface of peripheral immune cells by flow cytometry.

Results: Our results showed significant correlation between blood levels of IL-33 and eotaxin-1 (CCL11) and cognition in schizophrenia. Furthermore, increased cannabinoid receptor expression on lymphocytes and monocytes was significantly correlated with cognitive performance in patients with schizophrenia.

Conclusions: Inflammation is associated with worst cognitive performance in schizophrenia. Different mechanisms, including defective immunomodulatory pathways (e.g. cannabinoid system), seem to underlie this finding. In this context, the role of immune-based or anti-inflammatory strategies in schizophrenia will also be discussed.

Learning Objectives:

1. Describe the main immune/inflammatory changes in schizophrenia.
2. Identify the immune-based therapeutic targets for schizophrenia, and their potential clinical indication.

Literature References:

1. Campos-Carli SM, Araújo MS, de Oliveira Silveira AC, de Rezende VB, Rocha NP, Ferretjans R, Ribeiro-Santos R, Teixeira-Carvalho A, Martins-Filho OA, Berk M, Salgado JV, Teixeira AL. Cannabinoid receptors on peripheral leukocytes from patients with schizophrenia: Evidence for defective immunomodulatory mechanisms. J Psychiatr Res. 2017; 87: 44-52.
2. Campos-Carli SM, Miranda AS, Dias IC, de Oliveira A, Cruz BF, Vieira ÉL, Rocha NP, Barbosa IG, Salgado JV, Teixeira AL. Serum levels of interleukin-33 and its soluble form receptor (sST2) are associated with cognitive performance in patients with schizophrenia. Compr Psychiatry. 2017 Apr;74:96-101.

RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM IN SCHIZOPHRENIA: NEW TREATMENT OPPORTUNITIES?

David De Lucena, Federal University of Ceará

Individual Abstract: Involvement of Angiotensin II type 1 receptor (AT1R) in schizophrenia: a new target for drug repurposing. In the last decades, associations between angiotensin-converting enzyme gene polymorphism and susceptibility to schizophrenia were demonstrated. Brain renin-angiotensin system (RAS) is related to neuroinflammatory alterations mainly related to the activation of microglial angiotensin II type 1 receptor (AT1R). Hence, the dysregulation of brain RAS is associated with changes in glutamate release, reactive oxygen species (ROS) formation and activation of pro-inflammatory pathways, events also related to the pathophysiology of schizophrenia. In fact, a progressive increase in microglial activation from adolescence to adulthood was observed in schizophrenia patients, while in the plama increased levels of interleukin (IL)-1β, IL-6, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and soluble IL-2 receptor (sIL-2R) were detected. In the brain, AT1R activates NF-kB, a transcription factor for pro-inflammatory cytokines and ROS. Based on the possible

involvement of RAS in schizophrenia in the present study we sought to evaluate the expression of AT1R, NF-kB and cytokines in the hippocampus of mice neonatally challenged with the virus mimetic poly I:C and exposed to peripubertal stress, a neurodevelopmental two-hit model of schizophrenia. As secondary outcome we treated periadolescent animals with candesartan, an AT1R antagonist, to verify the prevention of schizophrenia symptoms. Male Swiss mice were challenged from the 5th to the 7th postnatal days (PN) with poly I:C 2 mg/kg or sterile saline, intraperitoneally. The animals were exposed during adolescence to unpredictable stress (US), on alternate days, from PN 35th to 42nd or not (NS). Another group of animals received oral doses of 0.3 mg/kg candesartan or saline from PN30-50. On PN70 the animals were submitted to behavioral determinations related to positive- (prepulse inhibition of the startle reflex – PPI), negative- (social interaction test) and cognitive-like (Y maze test) schizophrenia symptoms. Some animals were dissected for hippocampal removal and determination of immune-inflammatory alterations. Our results showed that the exposure to PolyI:C+US induced schizophrenia-related symptoms namely, PPI deficit, decreased social contacts and working memory impairment. These behavioral alterations were accompanied by increased hippocampal expression of IBA1 (a marker of microglial activation), AT1R, NF-kB, IL-4, IL-6, TNFα and pro-oxidative alterations. Candesartan prevented the behavioral and most of the neuro-immune alterations induced by PolyI:C+US exposure. In conclusion, pro-inflammatory mechanisms related to AT1R activation seems to be involved in schizophrenia neurobiology, being this receptor an important target for drug repurposing in this mental disorder. Finally, these are novel evidences not published yet.

Learning Objectives:

1. New Drugs for Schizophrenia.
2. R A A system in schizophrenia.

Literature References:

1. Saavedra, J. M. (2012). Angiotensin II AT 1receptor blockers as treatments for inflammatory brain disorders. Clinical Science (London, England: 1979), 123(10), 567–590. http://doi.org/10.1042/CS20120078
2. Benicky, J., Sanchez-Lemus, E., Honda, M., Pang, T., Orecna, M., Wang, J., et al. (2011). Angiotensin II AT1 receptor blockade ameliorates brain inflammation. Neuropsychopharmacology, 36(4), 857–870. http://doi.org/10.1038/npp.2010.225

REPURPOSING IMMUNOMODULATORY DRUGS TO TREAT SCHIZOPHRENIA

Danielle Macedo, Federal University of Ceara

Individual Abstract: Schizophrenia is associated with immune-inflammatory and oxidative stress mechanisms leading to the activation of the tryptophan catabolite (TRYCAT) pathway, which ultimately together with dysfunctional N-methyl-D-aspartate receptors (NMDAR) may cause neuroprogression and all symptom clusters of this mental disorder (1). Tryptophan metabolism is triggered by indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). By the enzymatic action of IDO tryptophan is converted to quinolinic acid, a potent neurotoxin, related to NMDA receptors activation. Conversely, TDO enzymatic activity is related to the synthesis of kynurenic acid, an NMDA and nicotine alpha7 receptors antagonist. While IDO is present in microglial cells, astrocytes present TDO. The activation of TRYCAT pathway is being related to schizophrenia symptoms such as cognitive decline. 1-Methyl-D-tryptophan (MDT) is an IDO inhibitor. MDT is being tested, in clinical trials, as an immunomodulatory strategy for cancer treatment. Melatonin, another immunomodulatory drug is metabolized by IDO while inhibiting TDO. In the present study, we evaluated the reversal of ketamine-induced schizophrenia-like behavioral and neurochemical alterations in mice, a validated pharmacological animal model of schizophrenia, by the administration of MDT (20

or 40 mg/kg, intraperitoneal) or melatonin (15 mg/kg, per os). We tested oxidative alterations by the evaluations of myeloperoxidase activity (MPO), reduced glutathione (GSH) and lipid peroxidation (LPO) as well as inflammatory changes, by the measures of interleukin (IL)-4 and IL-6 in brain areas related to schizophrenia neurobiology namely, prefrontal cortex (PFC), hippocampus and striatum. Risperidone was used as standard antipsychotic. Our results showed that ketamine triggered positive- (PPI deficits and hyperlocomotion), cognitive- (working memory deficits) and negative-like (social interaction deficits) symptoms of schizophrenia. These symptoms were accompanied by increased MPO activity, decreased GSH and increased LPO in all brain areas tested and by increments in hippocampal IL-4 and IL-6 levels. MDT and melatonin reversed all ketamine-induced behavioral alterations, while the antipsychotic risperidone did not reverse working memory deficits. MDT and melatonin reversed the alterations in MPO activity and GSH levels. Lipid peroxidation was reversed only by melatonin and risperidone. Risperidone was not able to reverse MPO alterations in the PFC and striatum. The immunomodulatory drugs and risperidone reversed the brain alterations in IL-4 and IL-6. The hippocampus and striatum of ketamine+melatonin-treated animals had marked low levels of IL-6. In conclusion, we observed that ketamine repeated administration besides triggering behavioral and brain oxidative alterations related to schizophrenia also induces neuroimmune changes such as increased MPO activity and increments in IL-4 and IL-6 levels. The IDO inhibitor, MDT and melatonin reversed ketamine-induced behavioral, pro-oxidant and neuroimmune alterations (2). These experiments open new avenues for the study of drugs targeting tryptophan metabolism in schizophrenia.

Learning Objectives:

1. Understand the importance of immune-inflammatory mechanisms in schizophrenia neurobiology and neuroprogression.
2. Show, based on preclinical findings, the importance of immunomodulatory drugs for the treatment of schizophrenia.

Literature References:

1. Anderson G, Maes M: Schizophrenia: linking prenatal infection to cytokines, the tryptophan catabolite (TRYCAT) pathway, NMDA receptor hypofunction, neurodevelopment and neuroprogression. Prog Neuropsychopharmacol Biol Psychiatry 2013; 42:5–19
2. da Silva Araújo T, Maia Chaves Filho AJ, Monte AS, et al.: Reversal of schizophrenia-like symptoms and immune alterations in mice by immunomodulatory drugs. J Psychiatr Res 2017; 84

SECOND-GENERATION GLUTAMATERGIC AGENTS FOR MAJOR DEPRESSIVE DISORDER*

George Papakostas, Massachusetts General Hospital

Overall Abstract: Depression is one of the most common medical conditions. Symptoms can lead to significant disability, which result in impairments in overall quality of life. Though there are many approved antidepressant treatments for depression—including serotonin reuptake inhibitors, tricyclic antidepressants and monoamine oxidase inhibitors—about a third of patients do not respond to these medications. Therefore, it is imperative for drug discovery to continue towards the development of novel compounds. The current pipeline of antidepressant treatments is shifting towards medications with novel mechanisms, which may lead to important, life-changing discoveries for patients with severe disease. Specifically, following the widespread clinical testing of intravenous ketamine for depression, several novel compounds are currently or have recently been studied that employ a variety of glutamatergic

mechanisms of action. After a review of unanswered questions in ketamine research, this session will then cover development efforts in this particular research area.

Learning Objectives:

1. At the end of this session, the audience will have a better understanding of unanswered questions in ketamine research for depression.
2. At the end of this session, the audience will have a better understanding of efforts towards developing second-generation glutamatergic agents for depression.

CLINICAL DEVELOPMENT OF INTRANASAL ESKETAMINE FOR TREATMENT RESISTANT DEPRESSION

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

Individual Abstract: Major depressive disorder (MDD) is the leading cause of disability worldwide. About 1/3rd of patients with MDD, do not adequately benefit from current antidepressants and are considered to have Treatment Resistant Depression (TRD)1. In the small number of patients with TRD that do improve current antidepressants, the improvement is short lived with nearly 70% of patients do not sustain that benefit and relapse within the following 3 months 1. There is a high unmet need for novel pharmacotherapies with fast onset of effect that can be sustained in patients with treatment-resistant depression (TRD), in order to reduce the disability from this disease.

Esketamine is a novel medication that modulate glutamate release2. This presentation will provide an overview of the esketamine development programs, unique challenges in developing glutamate modulators and provide a summary of the efficacy and safety data from the Phase 2/3 TRD program. Data from the Phase 3 TRD program demonstrate that treatment with esketamine nasal spray plus a newly initiated oral antidepressant compared to newly initiated antidepressant plus placebo nasal spray was associated with rapid reduction of depressive symptoms and with repeated individualized interval dosing, response was sustained. The long-term safety study showed that the esketamine doses studied were generally tolerated. Adverse events are typically seen on the day of dosing and resolve the same day. No new safety signal was seen with repeated weekly or every other week dosing up to 52 weeks.

Learning Objectives:

1. Provide learning on challenges in developing glutamate modulators.
2. Provide learning on individualizing dosing frequency with esketamine to maintain antidepressant response.

Literature References:

1. Rush AJ, Trivedi MH, Wisniewski SR, et al. 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
2. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, Thase ME, Winokur A, Van Nueten L, Manji H, Drevets WC. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: results of a double-blind, doubly-randomized, placebo-controlled study. JAMA Psychiatry. 2018;75(2):139-148.

CLINICAL DEVELOPMENT OF AV-101 FOR MAJOR DEPRESSIVE DISORDER

Mark Smith, VistaGen Therapeutics

Individual Abstract: Since the discovery that ketamine has rapid-acting antidepressant properties, there have been many efforts to produce a next-generation NMDA antagonist with

an improved risk/benefit ratio. Ketamine is an NMDA channel blocker that has robust efficacy but also produces psychotomimetic side effects. As a potential alternative, we have focused on the glycine modulatory site of the NMDA receptor with the aim of producing an antidepressant that decreases NMDA function without producing behavioral side effects. 7-chloro-kynurenic acid (7-Cl-KYNA) is a potent and specific full antagonist of the GlyB NMDA receptor, but it does not cross the blood-brain-barrier. Fortunately, L-4-chloro-kynurenine, or AV-101, is a synthetic amino acid prodrug which is transported into the brain where it is taken up by astrocytes and converted to 7-Cl-KYNA. AV-101 has been characterized in a variety of preclinical models where it was found to have rapid and sustained antidepressant effects comparable to that of ketamine. In contrast however, AV-101 did not induce locomotor sensitization or the rewarding and psychotomimetic effects of ketamine. We are now addressing whether this excellent risk/benefit ratio of AV-101 seen in rodents will translate to man.

We have administered AV-101 at doses up to 1440 mg per day for 14 days in Phase 1 studies in normal volunteers. Unlike ketamine, there has been no evidence of psychosis with AV-101. Interestingly however, there were spontaneous reports of "feelings of well-being" in about 10% of subjects which prompted us to target depression in Phase 2. Two Phase 2 studies are underway currently. NIMH is completing a small, cross-over study of AV-101 as monotherapy vs placebo in patients with major depressive disorder. We have also begun a much larger, proof of concept study (Elevate) of AV-101 as an adjunct antidepressant in patients who have an inadequate response to their current, standard antidepressant which will read out in mid-2019. In parallel we are also conducting a number of preclinical biomarker studies to document target engagement of AV-101 in the brain and compare and contrast its effects with those of ketamine. For example, although AV-101 has little effect on resting EEG in rats, the combination of AV-101 and ketamine produces a large, synergistic increase in gamma power. Using microdialysis, we find that both AV-101 and ketamine increase serotonin, norepinephrine and especially dopamine levels in rats. Surprisingly however, neither one increases glutamate. AV-101 also induces large increases in endogenous kynurenine and kynurenic acid but not quinolinic acid. The increased ratio of kynurenic acid, which is an NMDA antagonist, over quinolinic acid, which is an NMDA agonist, may be relevant to the potential antidepressant properties of AV-101. Our colleagues at Baylor and the Houston VA are currently determining if these biomarker effects are also seen in normal volunteers.

These studies suggest that AV-101 may prove to be a second-generation NMDA antagonist with antidepressant efficacy but without the side effects that complicate ketamine use.

Learning Objectives:

1. To understand the potential utility of a glycine B NMDA antagonist such as AV-101 as an adjunct antidepressant.
2. To compare and contrast the central physiological effects of AV-101 and ketamine on EEG, neurotransmitter release and kynurenine metabolites.

Literature References:

1. Zanos P, Piantadosi SC, Wu HQ, Pribut HJ, Dell MJ, Can A, Snodgrass HR, Zarate CA Jr, Schwarcz R, Gould TD, 2015. The Prodrug 4-Chlorokynurenine Causes Ketamine-Like Antidepressant Effects, but Not Side Effects, by NMDA/GlycineB-Site Inhibition. J Pharmacol Exp Ther. 355:76-85.
2. Wallace M, White A, Grako KA, Lane R, Cato AJ, Snodgrass HR, 2017. Randomized, double-blind, placebo-controlled, dose-escalation study: Investigation of the safety, pharmacokinetics, and antihyperalgesic activity of l-4-chlorokynurenine in healthy volunteers. Scand J Pain. 17:243-251.

OVERVIEW OF RAPASTINEL FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

Armin Szegedi, Allergan

Individual Abstract: Novel pharmacological approaches that modulate central N-methyl-D-aspartate receptors (NMDARs) are in development as rapid-acting antidepressants. Rapastinel, a novel NMDAR modulator with a unique mechanism of action, promises rapid-acting and long-lasting antidepressant effects in MDD with weekly intravenous (IV) injections, while suggesting a very good safety and tolerability profile with low propensity for dissociative/psychotomimetic side effects or abuse potential. Rapastinel received FDA Fast Track and Breakthrough Therapy designations based on Phase 2 data. Rapastinel's clinical development program for MDD has been designed to thoroughly evaluate both rapastinel's acute and long-term efficacy as well as the acute and long-term safety and tolerability. Conducting acute pivotal studies, maintenance study and long-term safety studies at the same time offered for a majority of trial participants the opportunity of long-term rapastinel treatment.

Two separate Phase 3 programs are being conducted for rapastinel: as adjunctive treatment to standard antidepressants in MDD (aMDD; US only, N=~1500) and as monotherapy (global; N=~2000), each with acute studies, maintenance study, and an opportunity for continued long-term treatment.

- Acute treatment: Three 3-week studies are conducted in aMDD (MD 01, 02, 03). Three 6-week studies evaluate rapastinel monotherapy (MD-30, -31, -32).
- Maintenance treatment: In maintenance studies, patients are stabilized with weekly rapastinel injections (8-16 weeks) to determine stable responders, who are then randomized to double-blind IV injections of rapastinel or placebo. In the aMDD trial (MD-04), patients receive weekly rapastinel, biweekly rapastinel, or placebo for up to 2 years of individual treatment. In the monotherapy trial (MD-33), patients receive weekly rapastinel or placebo for up to 1 year; this study also includes an individualized treatment arm, in which patients are assigned placebo or rapastinel in a blinded manner depending on weekly clinical assessments.
- Continued long-term treatment: Completers or patients who relapsed from MD 04 can continue open-label treatment in MD 06 for 1 year. Thereafter, they are offered continued rapastinel treatment in an extended access safety study (MD 99; US only). Completers or patients who relapsed from the US portion of MD-33 can also enroll in MD-99.

In a separate dedicated clinical trial rapastinel is also being evaluated as a treatment for MDD patients with imminent risk of suicide in addition to standard of care (MD-20; US only, N=~300).

First results from the acute aMDD trials are expected in the first half of 2019, available data will be summarized in the presentation.

Supported by Allergan plc.

Learning Objective:

1. To understand rapastinel's clinical development program as a novel rapid acting antidepressant with a unique pharmacology for the treatment approach for MDD.

CHARACTERIZATION OF THE AMPA RECEPTOR POTENTIATORS WITH LITTLE AGONISTIC EFFECTS TAK-137/TAK-653 AS POTENTIAL ANTIDEPRESSANTS

Haruhide Kimura, Takeda Pharmaceutical Company Limited

Individual Abstract: Purpose: The N-methyl-D-aspartate receptor antagonist ketamine has rapid-onset and sustained antidepressant activity in patients with treatment-resistant depression (TRD). However, its use is associated with unwanted side effects such as psychotomimetic effects. Activation of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors and subsequent activation of the mammalian target of rapamycin (mTOR) signaling pathway have been thought to contribute to the antidepressant efficacy of ketamine. Thus, AMPA receptor (AMPA-R) potentiators could be promising as novel antidepressants if issues of bell-shaped response and narrow safety margin against seizure can be overcome.

Content: We hypothesized that the agonistic property is related to the bell-shaped response and seizure risks and endeavored to discover novel AMPA-R potentiators with lower agonistic effects [1]. Here, we present findings on potent and selective AMPA-R potentiators with minimal agonistic effects, TAK-137 [2] and TAK-653. Our results suggest that these compounds may have antidepressant-like effects in the absence of psychotomimetic activity, reduced risks of bell-shaped responses, and a wider safety margin against seizure.

Methodology and Results: We found that Ca2+ influx in primary neurons, but not in a cell line expressing AMPA receptors, is suitable to characterize the agonistic effects of AMPA-R potentiators. Structural interference at Ser743 in the AMPA receptor was found to be a key for lowering the agonistic effects of some AMPA-R potentiators. TAK-137 and TAK-653 were discovered as novel AMPA-R potentiators with little agonistic effects. In both rats and monkeys, TAK-137 potently improved cognition with a wider safety margin against seizure [2]. In rat primary cortical neurons, both TAK-137 and TAK-653 significantly increased levels of phosphorylated and activated forms of mTOR and p70S6 kinase, and their upstream regulators Akt and extracellular signal-regulated kinase (ERK). Likewise, both compounds significantly increased brain-derived neurotrophic factor (BDNF) protein levels. In vivo antidepressant-like effects were evaluated using the novelty suppressed feeding (NSF) test and the reduction of submissive behavior model (RSBM) in rats. In the NSF test using rats, single-dose ketamine at 10 mg/kg, i.p., reduced latency to feed 24 h after treatment, and repeated treatment of TAK-137 at 0.3 mg/kg, p.o., for 3 days reduced latency to feed 24 h after final treatment. In the RSBM, ketamine at 30 mg/kg, i.p., reduced submissive behavior in rats 24 h after treatment; this effect was blocked by pretreatment with the AMPA receptor antagonist NBQX at 10 mg/kg, i.p., indicating that the antidepressant-like effect of ketamine is likely to be through AMPA receptor activation. Consistent with this finding, repeated treatment of rats with TAK-653 at 0.1 and 1 mg/kg, p.o., significantly reduced dominance levels in the RSBM. Unlike ketamine, however, both TAK-137 and TAK-653 did not induce a hyperlocomotor response in rats, which has been one of the behavioral changes linked with psychotomimetic side effects in humans.

Importance: These findings suggest that AMPA-R potentiators with lower agonistic effect, TAK-137 and TAK-653, may be promising drugs for the treatment of major depressive disorders, including TRD, with the potential for a superior safety profile. TAK-653 has been selected as an investigational agent.

Learning Objectives:

1. Describe a novel strategy for discovering AMPA receptor (AMPA-R) potentiators with lower risks of bell-shaped response and a wider safety margin against seizure [1, 2].

2. Review the antidepressant-like effect and psychotomimetic activity of TAK-137 and TAK-653, the AMPA-R potentiators with little agonistic effect.

Literature References:

1. Kunugi A, et al. J Pharmacol Exp Ther 2018; 364:377-389
2. Kunugi A, et al: Neuropsychopharmacology 2018. doi: 10.1038/s41386-018-0213-7

NONSTIMULANTS FOR ADHD: RATIONALE, EMERGING TREATMENTS, AND THE ROLE OF BIOMARKERS*

Jeffrey Newcorn, Icahn School of Medicine at Mount Sinai

Overall Abstract: Background: The expanding array of medications for ADHD offers enhanced opportunity for successful treatment, but clinical decision-making is complicated by notable differences in individual response. For example, although the majority of individuals will respond to either methylphenidate (MPH) or amphetamine (AMP), 30-40% will have preferential response to one or the other stimulant class, and a sizeable minority will have poor response or tolerability to both. While nonstimulants offer potential advantages in terms of abuse liability, duration of activity and potential for differential response, the effect size (ES) for nonstimulants has been decidedly lower and there have not been effective methods for predicting response/non-response. This presentation will offer a rationale for why nonstimulant medications for ADHD are needed, consider the range of options currently available or being developed, and illustrate how a biomarker-driven approach could aid in directing treatment selection.

Methods: The talks will include a review of relevant literature and presentation of research findings. The discussion will integrate the findings from the presenters and place them in context of clinical realities and needs for the future.

Results: 1) Dr. Jeffrey Newcorn will begin by introducing the session and present a rationale for the development and use of nonstimulants for ADHD across the lifespan. He will discuss advantages and limitations of stimulants, recent data related to nonmedical use and abuse, and clinical and neurobiological characteristics of existing nonstimulants. fMRI studies of existing nonstimulants illustrate both common and unique features of nonstimulants, and suggest that fMRI biomarkers (e.g., motor cortex activation during an inhibitory control task obtained off medication) can be used to predict of response to atomoxetine (nonstimulant) and preferential response to stimulants over atomoxetine (e.g., baseline striatal activation during the same task). 2) Dr. Timothy Wigal will present data on the nonstimulant pipeline, and how investigational nonstimulant drugs may potentially expand the nature of response and number of responders by targeting unique neurobiological mechanisms. 3) Dr. Josephine Elia will discuss the role of genetic biomarkers associated with ADHD phenotypes and RDoC constructs, illustrating the specificity of genetic biomarkers for different ADHD presentations. In particular, she will describe a subgroup of patients with ADHD found to have copy number deletions in the metabotropic glutamate receptor signaling pathway, and discuss initial results of a novel drug candidate, already developed for a different indication, for the treatment of youth with these biomarkers variants. Dr. James McGouogh will serve as discussant – amplifying issues related to the need for nonstimulant treatment in ADHD, advantages and limitation of existing medications, anticipated benefits of novel treatments, and the potential role of biomarker strategies in directing treatment selection.

Conclusions: Nonstimulant medications offer the potential to enhance our ability to treat ADHD across the lifespan. However, these medications will be most effectively used if they are paired with biomarker strategies to aid in matching clinical and neurobiological characteristics to treatment selection.

Learning Objectives:

1. Appreciate the range of potential neurobiological mechanisms which underlie existing and emerging nonstimulant treatments in ADHD.
2. Appreciate the potential utility of imaging and genetic strategies for predicting treatment response and better matching treatments to individual patient characteristics.

NONSTIMULANT ALTERNATIVES FOR ADHD: RATIONALE, PROMISES/LIMITATIONS, AND THE NEED FOR BIOMARKER PREDICTORS OF DIFFERENTIAL RESPONSE

Jeffrey Newcorn, Icahn School of Medicine at Mount Sinai

Individual Abstract:

Objective: To present a rationale for the use of nonstimulants for ADHD, highlighting their relative advantages and disadvantages, and illustrating the importance of developing biomarker-informed strategies for predicting optimal and differential response.

Overview of Presentation: Stimulants are highly effective, but their use is constrained by lack of optimal response and/or tolerability in a subset of individuals, and a number of other factors which will be reviewed. Data will be presented from a large two-site crossover comparator trial of atomoxetine (ATX) and methylphenidate (MPH) illustrating both the potential value and limitations of nonstimulants. We will examine: 1) Comparative effectiveness, preference for one or the other treatment, and how treatment sequence affected response; 2) Similarities and differences in mechanism of action of the two medications; and 3) fMRI predictors of clinical response.

Methodology: 1) Clinical study: Randomized, two-site, double-blind crossover study of 232 youth ages 7-17. Medications were titrated to optimal response over ~6 weeks using 4 dose levels for each drug. Multiple-group latent growth curve models were used to estimate the effects of medication and order of treatment on changes in ADHD symptom severity. Latent transition analyses examined the effect of order on responder status. Preference was determined under blinded conditions by a combination of direct contact and chart review. 2) fMRI studies: 36 youth in New York were scanned with fMRI before and after treatment in one block. Subjects performed a go/no-go task during fMRI as a probe of inhibitory control. Neural activity was modeled by contrasting activation during correct no-go minus correct go events. A regression model examined fMRI findings in context of clinical improvement. A secondary analysis examined fMRI profiles in 36 subjects (many but not all included in the prior analysis) off drug and treated with both MPH and ATX. Predictors of optimal and differential response were examined using a similar regression model.

Results: Clinical Study: MPH was superior to ATX, but with modest differences in ADHD symptom change between treatments, larger in Block 2. There were more responders to MPH and more non-responders to ATX. More families preferred MPH, but a sizeable minority preferred ATX. Preference was strongly related to excellent response and which medication was given first. fMRI Study: MPH and ATX had common therapeutic actions in motor cortex, and divergent therapeutic actions in task-positive and task-negative brain regions. Elevated caudate activation off drug was associated with preferential response to MPH over ATX. However, caudate activation did not predict MPH response overall.

Conclusions/Importance of the Talk: The clinical findings are consistent with results of prior parallel group comparator studies showing that MPH is overall superior to ATX. The fMRI findings confirmed the hypothesized common and unique mechanisms of MPH and ATX, and suggest that fMRI biomarkers can be used to predict of response to ATX (e.g., motor cortex activation during an inhibitory control task) and preferential response to MPH over ATX (e.g., baseline striatal activation during the same task). The existence of a sizable minority of ADHD

youth treated with both MPH and ATX who prefer ATX illustrates the potential importance of nonstimulants. The fact that ATX did better when given first and less well when given second, and did not bias against subsequent MPH response, challenges current treatment algorithms. Prediction of superior response to MPH over ATX in youth with elevated caudate activation off medication suggests the potential for personalized approaches to treatment selection.

Learning Objectives:

1. Attendees will appreciate limitations of stimulant treatment (as well as considerable advantages), and the potential value of non-stimulants.
2. Attendees will appreciate issues related to comparative effectiveness of stimulants and nonstimulants, common and unique mechanisms of action, and prediction of optimal and differential response using fMRI.

Literature References:

1. Newcorn J, Kratochvil C, Allen AJ, Casat C, Ruff D, Moore R, Michelson D. (2008) Atomoxetine and Osmotically Released Methylphenidate for the Treatment of Attention Deficit Hyperactivity Disorder: Acute Comparison and Differential Response. Am J Psychiatry Jun;165(6):721-30. Epub 2008 Feb 15.
2. Schulz, KP, Bédard, A-CV, Fan, J, Hildebrandt, TB, Stein, MA, Ivanov, I, Halperin, JM, Newcorn, JH. (2017). Striatal Activation Predicts Differential Therapeutic Responses to Methylphenidate and Atomoxetine. J Am Acad Child Adolesc Psychiatry. Jul;56(7):602-609.e2. doi: 10.1016/j.jaac.2017.04.005. Epub 2017 May 10. PMID: 28647012

ALTERNATIVES TO TYPICAL STIMULANTS AS EMERGING TREATMENTS FOR ADHD: WHAT'S IN THE PIPELINE?

Timothy Wigal, NeuroLife Sciences-1

Individual Abstract: Background: Stimulants are highly effective treatments for ADHD, but there are significant shortcomings related to time course and tolerability, and a significant percentage of individuals fail to respond. Stimulants are C2 controlled substances with known potential for diversion/misuse and abuse and can adversely impact the dopamine (DA) reward system via excessive release or inhibition of DA reuptake. These effects are thought to underlie the process of addiction. Therefore, treatments with a mechanism of action not involving the DA reward system, which still improve attention, are valued. This presentation will review pipeline non-C2 medications for ADHD, highlighting mechanism of action, trial results and potential for impacting treatment needs. Only information currently available and/or released for incorporation in this abstract is included; additional findings will be incorporated later.

Methods: A search of clinicaltrials.gov revealed 88 studies with at least Phase II results for ADHD. Almost all were new formulations of approved compounds; four were unique compounds with positive results (dasotraline (Sunovion), viloxazine (Supernus), centanafadine (Otsuka) and mazindol (NLS Pharma)).

Results: 1) Dasotraline is a triple reuptake inhibitor with greater affinity for DA than norepinephrine (NE), and serotonin (SERT) third. In a lab school study of 4mg/day dasotraline, 6 to 12-year-olds with ADHD evidenced clinically meaningful improvement compared to placebo on the primary endpoint, change in the SKAMP-combined score from baseline (effect size = 0.85, $p<0.0001$). A point of particular interest is the long half-life (47-77 hours), which could aid in covering the entire day better than existing drugs. The NDA filed for ADHD was reviewed in 2018 and not accepted; presumably further research will be forthcoming.

2) Viloxazine, a selective NE reuptake inhibitor, is a repurposed antidepressant that was in previous use in Europe. Supernus conducted an 8-week fixed dose phase 2 study of viloxazine,

in which 222 subjects were randomized to placebo or SPN-812 100, 200, 300, or 400mg/day. Significant improvements in ADHD-RS-IV Total score were observed for the 200, 300, and 400mg dose groups vs. placebo (P<0.05; ES=0.547, 0.596, 0.623). Tolerability was excellent, with only somnolence, headache, and decreased appetite occurring in > 15% of subjects. Based on these findings the medication is progressing to Phase 3.

3) Centanafadine (CTN) inhibits NE, DA and SERT reuptake in a ratio of 1:6:14.

In a Phase 2b clinical trial in adults with ADHD, CTN met its primary endpoint of a significant decrease in symptoms from baseline on the ADHD Rating Scale IV compared with placebo, with an effect size -0.66, p<0.001. The most frequently experienced treatment-related AEs were decreased appetite in (24.1%), headache (22.8%), and nausea (20.3%). Based on these findings, adult and pediatric Phase 3 studies are planned.

4) Mazindol is a SERT-, NE- and DA-reuptake inhibitor (SNDRI), with >99% binding at each; it is also a partial agonist of orexin-2, with 39% binding. In a phase II trial in adults with ADHD, weekly DSM5 rating scale measurements revealed a significant difference at Day 7 with at least squares mean difference (Active-placebo) of -13.2 at Day 42 and an effect size of 1.09. Adult and pediatric Phase 3 clinical studies are planned.

Conclusions: The above non-stimulant pipeline drugs for ADHD capitalize on a combination of known and novel mechanisms of action and have the potential to augment the existing therapeutic armamentarium. Potential advantages and disadvantages of each will be discussed, with a focus on how each can address unmet needs across the lifespan.

Learning Objectives:

1. Acquire an understanding of the kinds of drugs currently in the pipeline to treat ADHD.
2. Understand the difference between typical stimulants, atypical stimulants and non - stimulants in terms of efficacy in early phase clinical work and putative mechanism of action.

Literature References:

1. Goldman R, Adler, L, Spencer T, et al.: Dasotraline in children with Attention Deficit Hyperactivity Disorder: Results of a randomized, double-blind, placebo-controlled study. CNS Spectrums 2018; 23:102-109. doi.org/10.1017/S1092852918000615
2. Wigal T, Newcorn, JH, Handal N, et al.: A double-blind, placebo-controlled, phase II study to determine the efficacy, safety, tolerability and pharmacokinetics of a controlled release formulation of mazindol in adults with DSM-5 Attention Deficit Hyperactivity Disorder. CNS Drugs 2018; 32:289-301. doi.org/10.1007/s40263-018-0503-y.

GLUTAMATERGIC MODULATION IN ADHD YOUTHS HARBORING GENETIC VARIANTS DISRUPTING GLUTAMATERGIC NETWORK PATHWAYS

Josephine Elia, Nemours/A.I. duPont Hospital for Children

Individual Abstract: Overview of Presentation: Several neurotransmitter systems have been implicated in ADHD, with the dopaminergic system taking center stage in the recent past. Recent advances in genetics have led to expand our understanding, starting with the development of the Dopamine Transporter K-O mouse that showed a response to methylphenidate to the advent of genome-wide studies that allowed exploration of genetic variants without any a-priori hypothesis. Data from genetic and epigenetic studies providing support for glutamatergic dysfunction will be reviewed. In addition, data from a study of ADHD in the general population investigating the prevalence of mGluR variants will be presented as well as a pharmacotherapy trial of a glutamatergic modulator in ADHD youths, harboring mutations in genes disrupting the metabotropic glutamatergic network, will be presented.

Methodology: Identification of mGlur variants in a general population of ADHD youths (ages 6-17). Open-label, single blind-fixed placebo (wk1) in 30 youths identified with mutations in the metabotropic glutamatergic network, followed by 4-week dose-escalation of fasoracetam was done in tandem to a 24-hour PK study. Primary efficacy was measured by cumulative changes in CGI-I, CGI-S, Vanderbilt and Brief scores. Effects of fasoracetam were further examined on study subjects stratified by the presence of specific mGluR variants in Tier 1, Tier 2, or Tier 3 (more distantly related mGluR network genes).
Results: In 1876 ADHD youths (ages 6-17) in the general population, 22% were identified as carriers of mGluR variants.
In the treatment study, significant improvement was found in all four clinical measures by week 5 of study compared to week 1 (single blind placebo) with the strongest improvement noted in CGI-I scores. Actigraphy monitoring performed through the entire study period showed a net reduction in moderate to high intensity by week 5 compared to placebo week. Seventeen subjects with genomic deletions or disruptive duplications in Tier-1- mGluR genes and 7 subjects in Tier-2 mGluR genes showed superior response.
Conclusions: Clinical findings highlight the significance of identifying genetic variants that may be disrupting genes in neuronal network pathways implicated in ADHD. Specifically, in our studies that focused on glutamatergic network disruption, genetic prioritization and targeted medication treatment were critical contributors to clinical outcomes. Correlations with phenotyping will also be discussed.

Learning Objectives:

1. Increase understanding of glutamatergic dysfunction in ADHD.
2. Increase understanding of role of personalized treatment based on genetic variations in ADHD.

Literature References:

1. Elia J, Glessner JT, Wang K et al. Genome-wide copy number variation study associates metabotropic glutamate receptor gene networks with attention deficit hyperactivity disorder. Nature Genetics 2012; 44:78-84.
2. Elia J, Unsal G, Kao C, et al. Fasoracetam in adolescents with ADHD and Glutamatergic Gene Network Variants Disrupting mGluR Neurotransmitter Signaling. Nature Communications 2018; 9: 1-9.

Regulatory Wrap-Up Plenary
10:15 a.m. - 11:45 a.m.

REGULATORY WRAP-UP PLENARY
William Potter, National Institute of Mental Health

Overall Abstract: Participants will be able to ask questions to a panel of EMA and FDA representatives.

Javier Muniz, Food and Drug Administration
Michael Davis, US Food and Drug Administration
Valentina Mantua, Italian Medicines Agency