Presentation Abstracts

FOR THE 2017 APSARD ANNUAL MEETING

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Friday, January 13, 2017

Plenary Session:

ADHD and Autistic Spectrum Disorder. What Are the Relationships?
5:30 PM - 7:00 PM
Grand Ballroom

Chair: Gagan Joshi, Harvard Medical School, Massachusetts General Hospital

Overall Abstract: There is frequent comorbidity of Autism Spectrum Disorder (ASD) and Attention-Deficit / Hyperactivity Disorders (ADHD), which are both neuropsychiatric and neurodevelopmental disorders. The high co-occurrence rates suggest that there is overlap of genetic factors, cognitive dysfunctions, and functional and structural brain characteristics. These talks will discuss the evidence for shared factors involved in both ASD and ADHD. One in particular is the role of metabotropic glutamate receptors, which has been noted to play a crucial role in many neurodevelopmental disorders. We will also cover current research, clinical significance, and future directions for research and treatment of ASD and ADHD.

Learning Objectives:

- Appreciate the high rates of Autism and ADHD co-occurrence and their shared genetic factors, cognitive dysfunctions, and functional and structural brain characteristics.
- Gain understanding of the role of metabotropic glutamate receptors in the etiology and treatment of ADHD and Autism.

Role of Metabotropic Glutamate Receptors (mGluRs) in the Etiology and Treatment of ADHD and Autism
Hakon Hakonarson, Children's Hospital of Philadelphia and University of Pennsylvania

Abstract: My talk will address the role of metabotropic glutamate receptors in ADHD and autism as well as in other related neurodevelopmental and neuropsychiatric disorders; our work demonstrates that the glutamatergic neurotransmitter system (mGluRs) play an important role in multiple neurodevelopmental disorders.

Glutamate

- Major excitatory neurotransmitter in the brain activates ionotropic and metabotropic glutamate receptors.
- Metabotropic glutamate receptors (glutamate receptor metabotropic, GRM): G-protein-coupled receptors widely expressed in the CNS.
- GRMs: Modulate response to ionotropic glutamate receptors (e.g., NMDA and AMPA receptors) and response to other neurotransmitters, including dopamine and GABA.

- Multiple lines of evidence support glutamatergic involvement in ADHD and autism (e.g., imaging and pharmacology studies in ADHD and autism populations as well as animal model studies).
- Large-scale genetic association studies in humans suggest contribution of ADHD and autism risk genes involving glutamatergic signaling, including GRM genes: Elia et al, Nat Genet, 2012 (ADHD); Hadley et al, Nat Communic, 2014 (autism)

Fasoracetam (NFC-1) We licensed a non-selective mGluR agonist/activator molecule, a first in class, and obtained IND in the US in Nov 2014. The drug had been shelved after a phase III trial in Japan in patients with vascular dementia, following exposure to more than 1000 patients proven to be safe and well tolerated. We finished a clinical trial to assess the safety, pharmacokinetics and responsiveness of the glutamate receptor activator fasoracetam (NFC-1), in adolescents with complex neurodevelopmental phenotypes (ADHD, autism, anxiety, mood disorders and depression were most common); all study participants possessed disruptive mutations in GRM genes.

Clinical Trial Design The study was a Phase Ib study including 24 hour PK profiling, one week of placebo therapy and then 4-week dose-escalation therapy in 30 patients between 12-17 years of age with ADHD with 3/4 of subjects having comorbid phenotypes, including 7 subjects with autism. The parents were blinded with respect to placebo therapy. All patients harbored mutations in mGluR genes, defined as Tier-1/Tier-2 (primary mGluR mutation network) vs Tier-3 (reciprocal mGluR mutation network) mutations, and with double-blinded design with respect to mutation status. All subjects had a single dose pharmacokinetic (PK) period of a dose up to 800mg. After a week of single blinded placebo, subjects received open label NFC-1 with symptom-driven dose advancement up to 400 mg BID for 5 weeks. Clinical Global Impressions-Improvement (CGI-I) and Severity (CGI-S) scores and parental Vanderbilt scores, obtained each week, were analyzed by student's t-test.

Results: All subjects showed clinical improvement in CGI-S scores during 5 weeks of dose escalation; mean CGI-S 4.83 at baseline vs 3.86 at week 5 ($P<0.001$). Mean CGI-I scores also improved significantly showing moderate to much improvement (2.24) by week 5 ($P<0.001$). Subjects with mGluR variants in Tier 1/Tier 2 (n=24) genes showed the greatest improvement ($P<0.001$). There were no differences in the incidence of adverse events between placebo week and weeks on active drug.

Conclusions: Adolescents with ADHD and autism harboring GRM network mutations showed clinical improvement in symptoms in response to escalating dosages of NFC-1, a glutamate receptor activator. The drug is safe and well tolerated and improvement effects are dose dependent up to 400 mg BID. A 90 patient double blinded placebo controlled is near completion, 22Q DS study is ongoing and an autism dose fining study is about to begin. Trial Registration clinicaltrials.gov Identifier: NCT02286817

Attention Deficit Hyperactivity Disorder and Autism Spectrum Disorder: Two Manifestations of One Overarching Disorder?

Jan Buitelaar, Radboud University Medical Center

Abstract: Autism Spectrum Disorders (ASD) and Attention-Deficit / Hyperactivity Disorders (ADHD) are neuropsychiatric developmental disorders that frequently co-occur (Rommelse et al., 2010). The frequent comorbidity of both disorders is likely due to substantial overlap in genetic factors, cognitive dysfunctions, and functional and structural brain characteristics between ASD and ADHD (Rommelse et al., 2011). Both disorders are also hypothesized to share a common precursor, i.e. early deficits in executive attention (Johnson et al., 2015; Visser et al., 2016). This lecture will review the evidence for shared and unique genetic, cognitive and neural factors that are involved in ASD and ADHD and will argue that ADHD and ASD may be both manifestations of one overarching neurodevelopmental disorder. The last part of the lecture will discuss clinical implications of this view and outline further approaches for research, including interventions and prevention.

Saturday, January 14, 2017

Plenary Sessions:

New Perspectives on Neurobiology of ADHD
8:30 AM - 10:00 AM
Grand Ballroom

Chair: Jeffrey Newcorn, Mount Sinai Medical Center

Overall Abstract: This session will present results of studies using brain imaging to examine the multiplicity of brain regions and neural networks implicated in the pathophysiology of ADHD. It will consider similarities and differences in underlying neurobiology between ADHD and other disorders, and differences in neurobiology as a function of specific neuropsychological deficits, such as working memory. It will also examine the potential role of neurofeedback in attempting to modify regional activation and network function. Of considerable importance is the emerging role of the default mode network, the function of this region in relation to mind-wandering, and the coordinated relationship between default mode and task-positive network activity.

Learning Objectives:

- To understand results of studies examining the neurobiology of ADHD, and appreciate the multiplicity of brain regions implicated in the disorder.
- To understand the potential role of the default mode network to the pathophysiology of ADHD
- To understand similarities and differences in underlying neurobiology between individuals with ADHD who have working memory deficits and those who do not.
- To appreciate the potential emerging role of neurofeedback in modifying brain network activity and thereby produce therapeutic improvement in individuals with ADHD.

Neuroimaging of ADHD, Disorder-Specificity and Translation Into Neurotherapy
Katya Rubia, King's College London

Abstract: I will present our latest meta-analytic findings of structural and functional deficits in ADHD, the disorder-specificity of these deficits relative to other childhood disorders such as OCD and autism, and a translational neuroimaging study where abnormal brain activation is used as a target for a novel neurotherapy. Our most recent structural meta-analysis shows that ADHD children and adults suffer from reduced structure in the right basal ganglia and insula as well as ventromedial orbitofrontal cortex (Norman et al., 2016). Our meta-analyses of functional magnetic resonance imaging (fMRI) studies show cognitive domain-specific deficits in several dissociated fronto-striato-parietal and fronto-parieto-cerebellar networks during tasks of inhibitory control (inferior fronto-striatal networks) (Hart et al., 2013, Norman et al., 2016), attention (dorsal fronto-striato-parietal networks) (Hart et al., 2013) and timing functions (inferior fronto-parieto-cerebellar networks) (Hart et al., 2012). Furthermore, apart from poor activation of task-relevant networks, there is evidence for reduced deactivation of the default mode network in ADHD,

presumably reflecting mind-wandering, and both are associated with poor cognitive performance. Our comparative meta-analyses of structural and functional MRI deficits show that the basal ganglia and insula structure abnormalities and the inferior frontal underactivation are disorder-specific to patients with OCD (Norman et al., 2016) and autism (Lukito, in submission). An exciting new avenue is neurotherapy of abnormal brain activation. We conducted a proof of concept randomised controlled trial in 31 adolescents with ADHD, teaching them to self-upregulate the right inferior frontal cortex (rIFC) (N = 18 , active group) or the left parahippocampal gyrus (N = 13, control group) in 14 runs of 8 minutes of real-time fMRI Neurofeedback. Both NF groups showed significantly linearly progressive increased activation with increasing session numbers in their respective target regions relative to the other group. Both groups also showed reduced ADHD symptoms from pre to post and at an 11 month follow-up with no significant group differences. Only the active group, however, showed a transfer effect, where they showed increased activation in rIFC without the neurofeedback and showed significantly increased activation in rIFC in a Stop fMRI task, and improved at a trend-level in sustained attention task performance. The proof of concept study shows that rtfMRI-NF in ADHD children is feasible, safe, and efficacious short and longer-term. Given that region-specificity was not observed, future studies will have to replicate the findings against sham neurofeedback to rule out placebo effects.

References:

Hart H, Radua J, Mataix D, Rubia K (2012) Meta-analysis of fMRI studies of timing functions in ADHD. Neuroscience Biobehavioural Review, 36(10): 2248-2256.

Hart H, Radua J, Mataix D, Rubia K (2013) Meta-analysis of fMRI studies of inhibition and attention in ADHD: exploring task-specific, stimulant medication and age effects. JAMA Psychiatry 70(2):185-98

Norman, L, Carlisi, C, Lukito S, Hart H, Mataix-Cols, Radua J, D, Rubia, K (2016) A comparative meta-analysis of structural and functional brain abnormalities in ADHD and OCD. JAMA Psychiatry, 75

Neurodiversity in Adult ADHD

John Gabrieli, Massachusetts Institute of Technology

Abstract: ADHD is a complex neurodevelopmental disorder, and there is growing evidence that brain-behavior relations vary considerably across individuals who share the common diagnosis. We have used functional magnetic resonance imaging (fMRI) to characterize some of this neurodiversity. In one study, adults with childhood ADHD were divided into those who had a persistent diagnosis versus those who remitted from the diagnosis. Adults with persistent ADHD exhibited reduced resting-state functional connectivity of the default-mode network, whereas those with remitted ADHD were similar to control participants. In another study, ADHD adults with reduced working memory capacity exhibited atypical activation in fronto-parietal regions, whereas ADHD adults with unimpaired working memory were similar to control participants. These findings support the idea of considerable neurodiversity in adult ADHD, and future studies may use knowledge of that diversity to improve treatment outcomes.

Understanding and Assessing Executive Function vs. Core Symptoms in Adult ADHD
10:30 AM - 11:30 AM
Grand Ballroom

Chair: Lenard Adler, NYU School of Medicine

Overall Abstract: This session will present recent findings as to the importance of core DSM symptoms of Inattention (IA) and Hyperactivity-Impulsivity (HI) vs. symptoms of Executive Function (EF) and Emotional Control (EC) in Adult ADHD. Data will be presented as to the loading and impact of these core symptoms and co-travelling symptoms of EF and EC. The session will also present data as to the development and validation of dsm-5 version of the Adult ADHD Self-Report Screener (ASRS Screener); psychometrics of this updated version of this screener will also be presented.

Learning Objectives:

- To discuss the importance of core symptoms of inattention and hyperactivity-impulsivity vs. the co-travelling symptoms of executive function and emotional control deficits.
- To understand the scoring and symptoms contained in the dsm-5 version of the ASRS Screener.

Clinical Implications of Core Symptoms of Inattention and Hyperactivity/Impulsivity Vs. Executive Function (EF) and Emotional Control (EC) in Adult ADHD
Lenard Adler, NYU School of Medicine

Abstract: This presentation will review recent findings and implication of the loading of core DSM ADHD symptoms versus those of EF and EC. Data will be presented as to factor analysis of the loading of these symptoms in three cohorts of patients: community based, managed care and referred samples. Implications for clinicians regarding identification of the co-travelling symptoms of EC/EF and potential response to treatment will also be discussed.

The World Health Organization Adult ADHD Self- Reporting Screening Scale (ASRS) for DSM-5
Ronald Kessler, Harvard University

Abstract: Recognition that adult attention-deficit/hyperactivity disorder (ADHD) is common, seriously impairing, and usually undiagnosed has led to the development of adult ADHD screening scales for use in community, workplace, and primary care settings. But these scales are all calibrated to DSM-IV criteria, which are narrower than the recently-developed DSM-5 criteria. In this presentation we report the results of an analysis that created a much-improved version of the widely-used WHO Adult ADHD Self-Report Screening Scale (ASRS) for DSM-5. Probability subsamples of participants in two general population surveys (a household survey, n=119; a

managed care subscriber survey, n=218) that completed the full 29-question self-report ASRS, both subsamples over-sampling screened positives for adult ADHD, were blindly administered a semi-structured research diagnostic interview for DSM-5 adult ADHD. The Risk-calibrated Supersparse Linear Integer Model, a novel machine learning algorithm designed to create screening scales with optimal integer weights and limited numbers of screening questions, was applied to the pooled data to create a DSM-5 version of the ASRS screening scale. The new scale was then validated in an independent clinical sample of patients either treated or seeking evaluation at the NYU Langone Medical Center adult ADHD program and primary care controls (n=300). Blinded clinical diagnoses of DSM-5 adult ADHD were based on the semi-structured Adult Clinician ADHD Diagnostic Scale (ACDS). 44 NCS-R, 51 managed care, and 173 NYU Langone respondents met DSM-5/ACDS criteria for adult ADHD. A 6-question screening scale was found to be optimal in distinguishing these cases from non-cases. The operating characteristics of the screening scale were excellent at the diagnostic threshold in the weighted (to the 8.2% DSM-5/ACDS population prevalence) pooled general population samples (sensitivity=91.4%, specificity= 96.0%, AUC=.937, positive predictive value=67.3%). These characteristics were also very good at the same threshold when the screening scale was applied to the NYU Langone clinical validation sample (sensitivity=91.9%; specificity=74.0%; AUC=.829; positive predictive value=82.8%). The new screening scale is short, easily scored, detects the vast majority of general population cases at a threshold that also has high specificity and positive predictive value, and could be used as a first-stage screen in specialty treatment settings.

Symposia Sessions:

ADHD in College Students
1:00 PM - 3:00 PM
Chinese Ballroom

Chair: Kevin Antshel, Syracuse University

Overall Abstract: ADHD is a prevalent neurodevelopmental disorder that persists into adulthood. More than half of children with ADHD will attend a 2- or 4-year university, with prevalence rates of ADHD in college students estimated to be 5%. At least 25% of college students receiving disability services have ADHD. Thus, ADHD exists on college campuses. Despite ADHD existing in greater numbers on college campuses, our knowledge and understanding of ADHD in college students is relatively limited. This symposium brings together four clinical researchers who all have expertise in college students with ADHD. Individual talks with explore (a) understanding the longitudinal trajectory of ADHD in college and how best to intervene, (b) academic accommodations for college students with ADHD and what data and the law say about these accommodations, (c) stimulant medication misuse and diversion in college students with a focus on prevention within the primary care setting and (d) ADHD stigma and malingering in college students.
Learning Objectives:

- Increase participant understanding of how ADHD and its associated features and functional impairments unfold across the first four years of college, and are moderated/mediated by demographics and other variables of clinical interest.
- Understand opportunities for college student stimulant diversion prevention within the primary care setting.
- Understand current controversies in the provision of testing accommodations to college students with ADHD, making reference to relevant research where appropriate.
- Increase knowledge of associations between ADHD stigma and ADHD malingering in college students.

Presentations:
ADHD Stigma and Malingering in College Students
Kevin Antshel, Syracuse University

Longitudinal Outcome of College Students With ADHD
Arthur Anastopoulos, University of North Carolina at Greensboro

Stimulant Diversion Among College Students With ADHD and the Primary Care-Provider Relationship
Brooke Molina, University of Pittsburgh

Accommodations in College Students With ADHD
Larry Lewandowski, Syracuse University

Are Subsyndromal Manifestations of Disorders Meaningful?
1:00 PM - 3:00 PM
Grand Ballroom

Chair: Joseph Biederman, Massachusetts General Hospital

Overall Abstract: This symposium will focus on ongoing efforts to assess the clinical and scientific relevance of subsyndromal manifestations of psychiatric disorders afflicting the young. Dr. Biederman investigated the utility of subsyndromal scores on the Child Behavior Checklist (CBCL) Anxiety/Depression scale in identifying children at the highest risk for pediatric MDD from among the pool of children of parents with MDD. Subsyndromal scores on the CBCL Anxiety/Depression scale significantly separated the children at high risk for pediatric MDD from those at low risk in a variety of functional areas, including social and academic functioning whereas children at genetic risk without elevated CBCL Anxiety/Depression scale scores were largely indistinguishable from controls. These results suggest that the CBCL Anxiety/Depression scale can help identify children at highest risk for pediatric MDD. Dr. Faraone used familial risk analysis to examine the validity of subthreshold pediatric bipolar-I (BP-I) disorder in child

probands with full BP-I disorder, subthreshold BP-I disorder, ADHD, and healthy controls. Relatives of full BP-I and relatives of subthreshold BP-I probands had similarly elevated risk for BP-I disorder that were significantly higher than the rates in relatives of ADHD and relatives of control probands. These findings support the diagnostic continuity between subsyndromal and fully syndromatic states of pediatric BP-I disorder. Dr. Copeland's presentation uses data from a prospective, population-based study of 1420 participants assessed with structured interviews up to 6 times in childhood (ages 9 to 16; 6674 observations) for subthreshold psychiatric problems. Participants were then assessed 4 times in young adulthood (ages 19, 21, and 25 and 30; 4556 observations of 1273 subjects) for psychiatric outcomes as well as functional outcomes. At any given childhood observation, 19-21% of the sample displayed significant impairment secondary to psychiatric symptoms but did not meet criteria for a psychiatric disorder. By age 16, 30-35% of children displayed symptomatic impairment while never meeting criteria for a well-specified adult disorder. This group was at increased risk of meeting criteria for an adult psychiatric disorder or displaying a critical outcome in adulthood. These results support the conclusion that the number of children affected by psychiatric symptoms is far greater than those that meet criteria for a psychiatric disorder. Such children are at risk for later psychiatric and functional problems even if they never meet full criteria for a childhood psychiatric disorder. Dr. Gur will present data on efforts at advancing early identification and intervention of subthreshold psychosis and concomitant underlying neurobiological processes. Using data from the Philadelphia Neurodevelopmental Cohort that evaluated ~ 10,000 genotyped youths age 8-21 years ascertained through a pediatric network at Children's Hospital of Philadelphia. Subthreshold PS was noted in 12.3% of youths, age 11-21, and was associated with other clinical features including depression and anxiety as well as cognitive deficits relative to typically developing (TD) youth ,with most pronounced impairments on complex and social cognition domains. Multimodal neuroimaging showed that the PS group had a steeper decline in gray matter associated with development, impaired connectivity and diffusivity and aberrant pattern of fMRI activity during performance of a working memory and emotion recognition tasks: These alterations in brain-behavior measures evident early in the psychosis process can assist in early identification and intervention aimed at impacting developmental trajectories.

Learning Objectives:

- The audience will learn about the clinical and scientific importance of subthreshold diagnoses in pediatric psychiatry.
- The audience will learn about clinical examples of conditions in which a subthreshold diagnosis was specifically assessed.
- The audience will learn about the scientific and therapeutic implications of considering subthreshold diagnoses in practice.

Presentations:

Subthreshold Psychosis Symptoms in the Philadelphia Neurodevelopmental Cohort
Raquel Gur, University of Pennsylvania

The Consequences of Being Impaired but Undiagnosed
William Copeland, Duke University

Similar Familial Underpinnings for Full and Subsyndromal Pediatric Bipolar Disorder: A Familial Risk Analysis
Stephen Faraone, SUNY Upstate Medical University

Can Subsyndromal Manifestations of Major Depression Be Identified in Children at Risk?
Joseph Biederman, Massachusetts General Hospital

Symposia/Workshop Sessions:

A Mindfulness Intervention for ADHD in Adulthood
3:30 PM - 5:30 PM
Chinese Ballroom

Chair: John Mitchell, Duke University Medical Center

Overall Abstract: Mindfulness-Based Interventions (MBIs) involve the teaching of mindfulness meditation practices to target a variety of outcomes among different medical, psychiatric, and non-clinical populations. MBIs are particularly applicable for individuals with attention-deficit/hyperactivity disorder (ADHD) given that this treatment approach targets mechanisms that are also implicated in ADHD. Treatment outcome studies among adults diagnosed with ADHD demonstrate medium to large effect sizes for core symptoms and characteristic features of the disorder. There are currently few clinician materials to guide practitioners in administering an adapted MBI for adults diagnosed with ADHD. Therefore, the objectives of this workshop are to (a) define MBIs, (b) describe the rationale for applying MBIs to adults with ADHD, (c) establish the evidence-base of MBIs for ADHD, and (d) detail a MBI adapted for adults with ADHD: the Mindful Awareness Practices (MAPs) for ADHD Program. The latter will include a session-by-session description of the MAPs for ADHD Program.
Learning Objectives:

- Define mindfulness-based interventions (MBIs).
- Describe the rationale for applying MBIs to adults with ADHD.
- Establish the evidence-base of MBIs for ADHD in adulthood.
- Detail a MBI adapted for adults with ADHD.

Workshop Participant: John Mitchell, Duke University Medical Center

Current Issues and Mandates in Preschool ADHD
3:30 PM - 5:30 PM
Grand Ballroom

Chair: Scott Kollins, Duke University

Overall Abstract: ADHD is known to be a developmental disorder that emerges early in childhood, though there is controversy over how early the condition can be reliably diagnosed and the best approaches for treatment. This symposium will feature up-to-date information on the validity and reliability of ADHD diagnosis in preschool children, as well as what is known about safety and efficacy or both pharmacological and non-pharmacological treatments. We will also review data regarding how early behavioral and neurocognitive markers can predict outcomes later in life among young children at risk for ADHD. Finally, we will present a regulatory perspective on the importance of gathering data on the safety and efficacy of treatments in young children with ADHD.

Learning Objectives:

- Identify the primary treatment modalities with empirical support for managing ADHD in preschool aged children.
- Understand the developmental trajectories of young children at risk for ADHD and how they are related to clinical outcomes.
- Recognize the regulatory environment for approving treatments for preschool children with ADHD.

Presentations:

An Overview of Preschool ADHD: Developmental, Diagnostic, and Treatment Considerations
Scott Kollins, Duke University

Longitudinal Trajectories of Preschool Children at Risk for ADHD: Factors Associated With Variability of Outcomes
Jeffrey Halperin, Queens College

Clinical Trials in Preschool ADHD: A Regulatory Perspective
Graciela Gonzalez, FDA

Discussant: Tiffany Farchione, FDA

Sunday, January 15, 2017

Plenary Sessions:

Clinical and Epidemiological Studies of ADHD Across the Life Span: Does Age of Onset Matter?
9:00 AM - 10:30 AM
Grand Ballroom

Chair: Stephen Faraone, SUNY Upstate Medical University

Overall Abstract: This plenary session will present data to address recent claims that most cases of ADHD in childhood remit and that most cases of ADHD in adulthood are 'adult onset' cases. Several epidemiologic data sets will be presented along with discussion of the role of methodologic artifacts and the clinical implications of the findings.

Learning Objectives:

- Understand data about the persistence of ADHD from childhood into adulthood.
- Understand the basis of recent claims that most adult ADHD is 'adult onset' ADHD.
- Understand the methodological issues that weaken claims about adult onset ADHD.
- Understand the relevance of subthreshold youth disorders when evaluating 'adult onset' ADHD.

ADHD from Childhood Through Adulthood: Perspectives From a Population-Based Longitudinal Study
William Barbaresi, Boston Children's Hospital

Abstract: This presentation will focus on the following objectives:

1. Describe key findings from recent research on the adult outcomes for childhood ADHD, including persistence of ADHD into adulthood, stimulant treatment and growth, and psychosocial outcomes.
2. Enable pediatric clinicians to answer key questions about long-term outcomes posed by parents of children with ADHD.
3. Facilitate treatment focused on minimizing adverse outcomes and improving quality of life for young adults with a history of childhood ADHD.

Sailing in Troubled Waters: New Findings on ADHD Adolescent and Young Adult-Onset Trajectories and Their Childhood Predictors
Luis Rohde, Federal University of Rio Grande do Sul

Abstract: In this plenary session, I will discuss recent evidence from 4 different population studies suggesting that a significant proportion of adults with ADHD might have their onset of symptoms at adolescence or adulthood. Data indicating that these findings are not an artifact of methodological issues in the studies (e.g., not considering ADHD subthreshold symptoms in childhood, change of information source from childhood to adulthood and false-positive paradox) will be presented. In addition, I will discuss potential reasons for this different trajectory than the one found traditionally in clinical samples – the so-called child onset neurodevelopmental trajectory. Findings from clinical and population samples suggesting that there are not phenotypically differences according to ADHD age of onset before or after childhood will be also presented. Finally, I will discuss a work in progress in three of these cohorts and in the MTA data assessing potential predictors in childhood for adult ADHD. In the context of personalized medicine, we will test the performance of a predictor score that might work for adult ADHD as the Framingham score for CV disorders.

Genetic and Environmental Factors
11:00 AM - 12:30 PM
Grand Ballroom

Chair: Tanya Froehlich, Cincinnati Children's Hospital Medical Center

Overall Abstract: If you want to stay on the cutting edge of understanding genetic and environmental contributions to ADHD, this session is for you. Dr. Barbara Franke will review genetic variants recently implicated in ADHD by genome-wide association and next generation sequencing studies. Next, through her discussion of neuroimaging genetics research, bioinformatics approaches, and animal models, Dr. Franke will show how the statistical definition of a link between genes and ADHD can promote a more biological understanding of the roles played by specific genes. Furthermore, Dr. Joel Nigg will discuss environmental contributions to ADHD etiology, including the importance of using causally and genetically informative designs in environmental studies. Moreover, Dr. Nigg will show how gene by environment interactions and epigenetic effects remain important—perhaps central—possibilities for much ADHD etiology, particularly for common (shared) environments.

Learning Objectives:

- Describe the contribution of genome-wide association, next generation sequencing, genetic neuroimaging, bioinformatics, and animal model approaches to understanding the genetic underpinnings of ADHD.
- Describe the use of epigenetic approaches, gene-environment interactions, and causally and genetically informative designs to elucidate the contribution of environmental factors to ADHD etiology.

ADHD and the Environment: Why and How Should We Study ADHD's Environmental and Epigenetic Etiology?
Joel Nigg, Oregon Health & Science University

Abstract: Twin studies demonstrate that ADHD has a substantial heritability of liability, but this is often misunderstood to mean heritability of disease and thus irrelevance of environmental etiologies. The genetic influences are complex, likely a mix of large but rare mutations and many common mutations of small effect. Within that framework, gene by environment interactions and epigenetic effects remain important—perhaps central—possibilities for much ADHD etiology, particularly for common (shared) environments. At the same time, while an extensive literature documents environmental risk factors for ADHD, most of that literature does not use genetically or causally informative designs, leaving it unclear which environmental effects are actually exerting causal influence. To resolve this, causally and genetically informative environmental studies are recommended. Illustrations that differentiate causal from non-causal environmental risk factors are provided. Finally, the mechanism of action may well be epigenetic, and the outlines of an epigenetic approach are noted.

The Biology of ADHD: From Basic Science to Application in the Clinic
Barbara Franke, Radboud University Medical Center

Abstract: These are great times in psychiatric genetics! Through international collaboration and technological progress we are finally starting to find the genes for psychiatric disorders. Using genome-wide association and next generation sequencing, we identify genes and genetic variants, that are statistically correlated with disease. I will discuss some recent findings from such studies for ADHD.
How can we go from the statistical definition of a link between gene and disease to a more biological understanding of the involvement of a genes and its variants? And how can we make such findings useful for the patient? In the second part of my presentation, I will discuss different approaches that we employ, and what their contribution to solving the puzzle of ADHD at different levels of organismal complexity can be. Approaches include neuroimaging genetics research - linking genetics, brain, and behavior, bioinformatics approaches that may clarify the biochemical processes affected and enable lead identification for treatment innovation, and work in animal models. For the latter, my group has recently pioneered the use of Drosophila melanogaster, the fruit fly, as a cheap and versatile small animal model for ADHD.

Symposia Sessions:

A Data-Driven Approach to Understanding ADHD in Females Across the Lifespan
2:30 PM - 4:30 PM
Chinese Ballroom

Chair: Kathleen Nadeau, Chesapeake ADHD Center of Maryland

Overall Abstract: ADHD exists within a context, be it neurological, maturational, social or hormonal and all of these various contexts have an impact upon the presentation of ADHD in

females. This symposium will provide updates on the range of sex differences in ADHD that have been explored with presentations focusing on:

- Sex differences in the unfolding of ADHD symptom patterns related to striking differences in patterns of brain development.
- Differences in social impairments in girls with ADHD in contrast to boys.
- Hormonal changes in peri- and post-menopausal women that sometimes lead to a worsening of executive function (EF) in women.
- Findings from a prospective, longitudinal study of girls with ADHD showing a much greater risk for a wide range of adverse psychiatric outcomes in young adulthood compared to girls without ADHD.

Learning Objectives:

- Participants will be able to identify the elevated risk for multiple serious comorbid conditions as girls with ADHD enter young adulthood.
- Participants will be able to explain the differing patterns of neurological development in male and female brains and how these differences affect the presentation of ADHD at different developmental stages.
- Participants will be able to identify how changing hormonal levels in the brains of females can impact executive functioning.
- Participants will be able to explain how social problems in females with ADHD change from childhood, through adolescence and into adulthood.

Presentations:

Executive Dysfunction at Menopause: Behavioral and Imaging Correlates
Neill Epperson, Department of Psychiatry, University of Pennsylvania

Eating Pathology among Adolescent and Emerging Adult Women with ADHD
Amori Mikami, University of British Columbia

Sexual Dimorphism in the Neurobehavioral Development of ADHD
Mark Mahone, Kennedy Krieger Institute

Long Term Outcomes of Girls With ADHD: A Controlled Study
Joseph Biederman, Massachusetts General Hospital

Stimulant Vs. Nonstimulant Treatment of ADHD and Related Disorders
2:30 PM - 4:30 PM
Grand Ballroom

Chair: Frances Levin, Columbia University Medical Center

Overall Abstract: The large majority of youth with ADHD who are treated with psychostimulants have a significant reduction in symptoms, but a smaller number achieve normalized function. This presentation will review the mechanism of action of the different stimulant and nonstimulant medications for ADHD, and present clinical trials data that have examined comparative efficacy and effectiveness of the different medications. It will also examine data regarding relative efficacy of the different medications when given before or after other treatments, to inform on sequencing of treatments and the development of treatment algorithms.

Learning Objectives:

- To understand similarities and differences in mechanism of action of stimulant and non-stimulant medications for ADHD.
- To appreciate differences in comparative effectiveness between stimulant and nonstimulant medications for ADHD.
- To understand the relative impact of prior treatment on efficacy of the different medications.
- To understand the potential impact of comorbid aggression, tic disorders and substance abuse on treatment selection in individuals with ADHD.

Presentations:

Stimulants or Nonstimulants for ADHD: Comparative Effectiveness, Differential Response and Algorithm Development
Jeffrey Newcorn, Mount Sinai Medical Center

How Do We Best Treat Individuals With ADHD and Substance Use Disorders?
Frances Levin, Columbia University Medical Center

ADHD, Stimulants and Tics: Much Benefit, but How Much Risk?
Barbara Coffey, Icahn School of Medicine at Mount Sinai

Are There Different Effects of Stimulant and Non-Stimulants on Aggression in Patients with ADHD?
Steven Pliszka, UT Health Science Center at San Antonio

Friday Poster Abstracts

Friday Poster Session
7:00 PM – 8:30 PM
East & State Ballroom

**Denotes presenting author*
***Denotes a Poster Tour Abstract*

**F1. Absence of Alignment of Symptom Response/Remission With Functional Outcomes in Children and Adolescents Following Treatment for ADHD

Margaret Weiss*[1], Ann Childress[2], Greg Mattingly[3], Earl Nordbrock[4], Robert J. Kupper[4], Akwete Adjei[4]

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Background: Clinical trials that evaluate treatments for attention-deficit/hyperactivity disorder (ADHD) in children and adolescents generally report success as a change in symptom score. There remains a need to better understand how a pharmacotherapeutic intervention for ADHD might impact functional outcomes and the relationship between change in symptoms and change in functioning. We evaluated functional characteristics of children with ADHD and compared the relationship between clinical response/remission and functional outcomes after 11 weeks of treatment with MPH-MLR (methylphenidate hydrochloride extended-release).
Methods: Data used in this post-hoc analysis were from the open-label (OL) dose-optimization phase (11 weeks) of a pivotal trial. Weiss Functional Impairment Rating Scale (WFIRS) and ADHD Rating Scale (ADHD-RS-IV) were assessed at Baseline and end of OL. Definitions: symptom improvement (≥30% decrease in ADHD-RS-IV total score); symptom remission (ADHD-RS-IV total score ≤18); functional improvement (change in WFIRS total ≥0.25 [minimally important difference]); functional remission (WFIRS total ≤0.65).
Results: At baseline, ADHD-RS-IV mean total scores for treatment naive (n=148) were similar to those for previously treated (n=73; 36.0 vs 36.4); mean WFIRS total indicated more functional impairment for treatment naive (0.82 vs 0.70, p=0.01). WFIRS total and individual domain scores were similar for children and adolescents. ADHD presentation most prevalent: combined (2/3 of patients) with predominately inattentive being most of the remaining 1/3. Functional impairment was prevalent across WFIRS domains; greatest impairment in Learning (Learning 1.73, Family 0.81, School Behavior 0.62, Life Skills 0.98, Self-concept 0.82, Social 0.64, Risky Activities 0.36). At OL end, statistically and clinically significant improvement in all functional domains was noted (p<0.001): largest improvement was in Learning (1.03 at OL end). 54% of patients had functional improvement at OL end, yet 43% of patients with symptom improvement did not have functional improvement. Although mean WFIRS total score at OL end for those with symptom remission was 0.45, 19% with symptom remission remained functionally impaired.
Conclusions: Children and adolescents with symptom improvement or remission following treatment with MPH-MLR did not consistently show functional improvement or normalization,

which demonstrates the importance of including functional outcomes in clinical studies. Children who continue to show significant functional impairment despite symptom normalization may require additional therapeutic interventions.

F2. Sleep Patterns Among Children With ADHD and ASD Participating in a Summer Treatment Program: Preliminary Findings

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Background: Children with ADHD and ASD often experience sleep disturbances, including impairments in sleep onset and duration relative to their peers (Hvolby et al., 2008; Cortese et al., 2009). Sleep problems have been shown to exacerbate core symptoms of both ADHD and ASD (Malow et al., 2006). Pharmacological and behavioral treatments and their combination are often utilized to target ADHD symptoms (MTA Cooperative, 2004; Virués-Ortega, 2010). Summer treatment programs for ADHD which include behavioral and medication components, also increase physical activity, which may also contribute to improvement in core symptoms as sleep (Best, 2010; Berwid & Halperin, 2012; Grassmann et al., 2014; Sowa & Meulenbroek, 2012). The current study examined relationships between sleep onset latency (SOL) and sleep quality, and the impact of activity level before, during and after participation in an STP. SOL is hypothesized to be associated with poorer sleep quality and greater morning fatigue; and SOL is hypothesized to decrease and sleep quality will improve during camp.

Methods: The sample included children participating in Apex day camp, a 5-week intensive Summer Treatment Program (STP) through the University of Washington Autism Center in collaboration with Seattle Children's Hospital. This sample include 53 children, 13.2% female and 86.8% male, with an average age of 8.6 (SD=1). Caregivers completed a daily sleep diary, detailing the child's previous day including activity level, whether they had a nap, whether they had caffeine, their bedtime routine, SOL, qualitative report of child's sleep, and morning affect. Children were also queried on the quality of their sleep (e.g. "how well did you sleep." This measure was completed 4 days/week for two separate weeks at each time, before, during, and after camp. Analyses examined these measures across the sample and throughout camp.

Results: According to parent and child ratings, longer sleep latency was associated with poorer sleep quality ($r= -0.35$, $p < 0.000$), and increased morning fatigue ($r= 0.140$, $p < 0.05$). Poor sleep quality was associated with morning fatigue ($r= -0.407$, $p < 0.000$). Multiple regression analysis results suggest longer sleep onset latency predicts poorer sleep quality ($\beta = -.0126$, $p <.001$). Stimulant use did not significantly predict sleep quality ($\beta = .148$, $p <.242$). There was a significant difference of SOL before and during STP, ($F(2,218) = 4.625$, $p = .011$). Post hoc analyses suggest SOL was significantly lower during camp compared to before (22.3 ± 18.8 min, $p = .04$).

Conclusions: Consistent with previous research, longer sleep onset latency was associated with lower sleep quality and increased morning fatigue for children with ADHD and ASD prior to participating in a STP. Preliminary findings suggest that participating in a summer day camp is associated with slightly reduced time falling asleep. Further analyses will directly investigate the impact of STP factors, including physical activity on sleep. This research may lead to the importance of increased activity as a treatment component for children with neurodevelopmental disabilities such as ADHD and ASD. Increases in levels of activity may lead to improved sleep

and subsequently better treatment outcomes. Further clinical and treatment implications are discussed.

F3. Further Evidence of Morbidity and Dysfunction Associated With Subsyndromal ADHD in Clinically Referred Children

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Background: While the diagnostic criteria for ADHD have evolved over the years, irrespective of the nosological context, some children with impairing ADHD symptoms fail to meet full diagnostic threshold for the disorder. While a small literature documents that youth with subthreshold ADHD experience significant symptomatic and functional impairments, the available literature is entirely based on community samples. The main aim of this study was to evaluate the morbidity and dysfunction of subsyndromal ADHD in the clinical setting.

Methods: Subthreshold and full ADHD subjects were derived from consecutive referrals (n=2,947) to a pediatric psychopharmacology program at a major academic center. This clinic sample is "unselected" as children were referred for psychiatric evaluation for behavioral and emotional difficulties and not for evaluation of any specific disorder. There was no selection bias based on social class or insurance restrictions. Healthy control subjects were derived from two identically designed longitudinal case-control family studies of youth of both sexes with and without ADHD. Psychiatric assessments of subjects relied on the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Epidemiologic Version (K-SADS-E). The Child Behavior Checklist (CBCL) was used to assess dimensional measures of psychopathology. Social functioning was assessed using the Global Assessment of Functioning Scale (GAF), CBCL social functioning scales (Activities, Social, and School), and the Social Adjustment Inventory for Children and Adolescents (SAICA). Cognitive ability was assessed using the Wechsler Intelligence Scale for Children – Revised Version (WISC-R) and academic achievement using the Wide Range Achievement Test (WRAT).

Results: Of the 1,931 children with a diagnosis of ADHD, 140 (7%) were diagnosed with subthreshold ADHD. Forty-eight percent of subthreshold ADHD subjects had an age at onset ≥ 7 years old and 73% had insufficient symptoms. Subjects with Subthreshold ADHD differed from Controls on the mean number of comorbid disorders, individual comorbid disorders, CBCL clinical and social functioning scales, GAF, SAICA, cognitive, achievement, and educational scores. In contrast, subjects with Subthreshold ADHD had a significantly higher proportion of females, were older, were of higher SES status, had less family conflict, and had less perinatal complications compared to the full ADHD subjects.

Conclusions: Clinically referred children failing to meet full threshold diagnosis for ADHD due to either insufficient symptoms or later age at onset, have highly similar patterns of correlates as those with the full syndrome including high rates of comorbid psychopathology, interpersonal, cognitive, and school functioning deficits. These results extend to clinical samples previously reported findings in non-referred samples documenting the high morbidity and disability associated with subthreshold ADHD. Female sex, higher SES status, less family conflict, and less perinatal complications distinguished subthreshold from full ADHD cases.

F4. A Meta Analysis of ADHD and Increased Risk for Suicide

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Background: ADHD is a common condition, affecting one in 20 children in the United States. While ADHD's effects on attention and impulsivity are well known, the unique risk factors correlated with ADHD have received less attention. The current research study attempts to remedy that disparity by performing a meta-analysis of published empirical research comparing the rate of suicide risk among individuals with ADHD to the general population. Accurate information about risk factors will allow clinicians to make evidence-based risk assessments when working with clients with ADHD, and may inform further research into effective interventions for suicide prevention among ADHD populations.

Methods: A review of the literature was gathered to examine the relationship between ADHD diagnosis and suicidality. Only studies that included quantitative measures of suicide risk and clinically diagnosed ADHD were included. Researchers analyzed 6 articles from 2010-2015 delineating the relationship between aspects of suicidality and attention deficit/hyperactive disorder. Specifically, researchers compiled data from the studies on rates of suicidal ideation, suicide plan, suicide attempt and suicide completion among participants with ADHD, and then compared those rates to normative data from the general population. As previously mentioned, researchers did not include statistics regarding nonsuicidal self-injury due to a previous meta analyses on that topic conducted by Allely. Allely used 15 articles in her study examining the association between ADHD and self-harm. Using a PRISMA-P systematic review of literature, she found sufficient evidence that ADHD is a risk factor for self-harm. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) is a 17-item checklist designed to aid researchers by recommending what items should be addressed in a systematic review.

Results: Our findings yielded results consistent with the available literature that posits ADHD is correlated with a higher risk for suicidality. Researchers gathered population size, breaking down participants with ADHD and comparison group, and number of people that reported suicidal ideation, attempt, plan, and completion in each study. Using SPSS for Mac, researchers ran an odds ratio by computing the number of total participants who reported risk for suicide in both ADHD and comparison groups for suicidal ideation across four studies, suicide plan across one study, suicide attempt across five studies, and suicide completion from one study. Across studies, suicidal ideation was elevated (OR 2.611, 3.695, 4.668, 5.777), suicidal plan was not significantly elevated (OR 2.294), suicidal attempt was elevated (OR 4.547, 3.445, 3.609, 5.192, 3.620), and suicidal completion was elevated (5.910) when compared to non-ADHD populations.

Conclusions: These results suggest that clinicians who treat clients with ADHD should be aware of the elevated suicide risk among clients with ADHD and ensure that they are well-trained in evidence-based methods to assess and treat suicidality. The field would benefit from further research to develop suicide prevention interventions that are specifically designed for clients with ADHD, such as cognitive behavioral interventions to reduce the impulsivity that is a common feature in ADHD presentations.

F5. ADHD and Temperament

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Background: Studies have frequently reported the high comorbidity rate between ADHD and bipolar disorder (Faraone et al., 1997), whereas the juvenile bipolar disorder rate in the general population is around 0.3% (Kent and Craddock, 2003). There are four plausible explanations of this high rate of comorbidity (Klassen et al., 2010).

1. A chance phenomenon;
2. An artifact of overlapping criteria;
3. Due to a common diathesis that leaves patients vulnerable to separate illness;
4. Symptoms of ADHD that precede the onset of bipolar disorder represent a prepubertal expression of an affective episode.

In this study, we examined the 3rd explanation using TEMPS-A, mainly focusing on cyclothymic and hyperthymic temperament (Akiskal et al., 1987).

Methods: The present study had two groups: (1) 43 ADHD; and (2) 28 adult (control). The adult group were recruited from several Japanese companies or facilities. The first author administered the Japanese semi-structured diagnostic interview for adult ADHD (Takeda et al., 2015).
Firstly, using cut-offs of TEMPS-A for cyclothymic and hyperthymic temperaments, the ratio of each temperament were compared by chi-square test. Secondary, scores in each temperament were compared by t-test. Lastly, in order to exclude the possibility that difference can be explained by overlapping criteria between ADHD and the relevant temperament, t-test and effect size were calculated after omitting 2 items from each temperament subscale.

Results: In chi-square test, the ADHD group has significantly higher ratio of cyclothymic temperament (97.67%) than that of the control group (75.00%; $p = 0.005$). On the other hand, the ratio of hyperthymic temperament was not significantly different between ADHD and control groups.
Out of 31 patients with inattentive ADHD and 10 patients with combined or hyperactive-impulsive ADHD, 31and 9 patients have cyclothymic temperament, respectively, and 11 (35.48%) and 8 (80.00%) patients have hyperthymic temperament, respectively ($p = 0.01$).

In t-test, the ADHD group has higher score in cyclothymic temperament score than the control group does even after omitting 2 items and there is no significant difference in scores between 2 groups.

Conclusions: Cyclothymic temperament seems to be more related to ADHD than control subjects. This tendency remained even after omitting 2 overlapping items between cyclothymic temperament and ADHD symptoms. Additionally, hyperthymic temperament seems to be more related to combined or hyperactive-impulsive ADHD than inattentive ADHD. These results partly explain the higher rate of comorbidity of bipolar disorder in ADHD. However,
there are more items in TEMPS-A which were not omitted in this study but has similarity with ADHD symptoms (e.g. 52. I love to tackle new projects, even if risky.). Generally, items in cyclothymic and hyperthymic temperament are similarto inattentive and hyperactive-impulsive symptoms in ADHD, respectively.

Temperament is the combination of mental, physical and emotional traits of person which can be observed from childhood, whereas symptoms of developmental disorders are based on innate brain dysfunction. Are similarities between these temperaments and ADHD symptoms just a coincidence? We can see these similarities from different perspective. Possibly the descriptions of cyclothymic and hyperthymic temperament could be developed, based on the symptoms in 2 subtype of ADHD spectrum.

F6. Clinically Analogous Dysregulation Behaviours in a Robotic Systems-Control Model of ADHD and Bipolar Disorder

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Background: Robotic development was selected for physical implementation of an experimentally-observable, operational model of behavioral systems-control theory in proposed clinical translation. A rigorously derived intuitively qualitative systems heuristic was previously proposed for this purpose was previously shown to be consistent with DSM criteria and on retrospective chart review for ADHD and Bipolar Disorder (BPD). The heuristic considers intuitive systems analogs for clinical behaviour such as predictability, time invariance, boundedness and disturbance rejection. This characterized ADHD as a predictable, dysregulated stable system in contrast to the unpredictable variabilities that identify BPD as unstable.

Methods: An autonomous 2-wheeled robot was constructed to implement self-balancing as a prototypic dynamically controlled behavior. Hardware abstraction of behavioral feedback control included position and acceleration sensors, motors and a microprocessor unit. Software coded for a Proportional-Integral-Derivative (PID) error feedback control algorithm. No other behavior was programmed. Battery power was regulated for fixed output. 4 identical robots were produced then tuned randomly by computer to stable, dysregulated and unstable states. 3 evaluators then observed for sustained balance, falls, positional drift, and collision response in multiple different structured and unstructured contexts for each state.

Results: Observed behaviors were state dependent, but otherwise indistinguishable between robots and across observers. Optimally stable robots sustained balance and position regardless of context. No collisions or falls occurred. Manual disturbance rejection was robust. Dysregulated (ADHD) robots sustained balance with greater movements across a wider base and roamed positionally. Balancing settled or deteriorated consistently in some contexts. They were reactive to collision, but quick to settle. They did not fall and tended to wander and settle into positions of higher stability. Unstable state (BPD) robots achieved but not sustain various states of balance, they accelerated and fell often and reacted violently to collision. Behavior was overall unpredictable, non-repeatable and inconsistent independent of context.

Conclusions: Operational robotic modelling of behavioral control dysregulation yielded observations consistent with the clinical systems heuristic for conceptualization of ADHD and BPD as stability disorders. The emergence of additionally observed intuitively analogous clinical systems behavioral correlates consistent with these diagnoses such as contextual and structural responsivity in the dysregulated Robotic model of ADHD reinforces this approach. Reproduction of this range and mix of clinically corresponding phenomena achieved through alteration of the systems' stability alone may further imply that these and other core symptoms of ADHD are more

appropriately attributed to regulatory rather than executive mechanisms. Model observations may also suggest that the ferocious reactivity of BPD represents an unbounded unstable response, rather than the dysregulated, but stable and bounded irritability of ADHD. These findings encourage further exploration and development of practical systems science applications to clinical medicine.

F7. Practice Patterns of Primary Care Providers and Older ADHD Patients

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Background: Primary care providers (PCPs) are reporting an increase in the demand for ADHD evaluations from adult patients in almost every decade of life when cognitive change occurs. At the University of Washington Primary Care Network, twenty PCPs serve as ADHD specialists across 12 clinics in the Puget Sound region. The goal of this project was to identify diagnostic challenges associated with the older patients seen by one of these ADHD specialists.

Methods: Electronic data was mined from 9,355 clinic visits for 3,114 patients seen by the ADHD specialists from June, 2013 through July, 2016. After completing a qualitative review, significant co-morbidities, demographics and medication were statistically analyzed. Patient categories and diagnostic challenges were then identified.

Results: Of the patients seen, 129 patients were age sixty and older. There were more females (67%) than males (33%). Forty-nine percent smoked or were former smokers and 39% reported drinking alcohol. Data was not available on recreational drugs. No childhood records were included in any of the charts.

The most influential common conditions (range of 2 to 23) recorded were 'other psychiatric diagnoses' (67%), insomnia or OSA (62%), heart disease (48%) and pain (40%). The most frequent influential chronic medications were antidepressants (48%), sleep aides (45%), heart medication (42%) and narcotics (40%).

Four categories were identified to further evaluate the patients according to the presents/absent of an ADHD diagnosis and ADHD medication. There were 36 patients (28%) with the diagnosis of ADHD and an ADHD medication (Dx with Med). Twenty-three patients (17%) had an ADHD diagnosis but no ADHD medication (Dx without Med). Sixty-six patients (51%) did not have an ADHD diagnosis or ADHD medication on their chart (No Dx and No Med) and four patients had no diagnosis but were prescribed an ADHD medication (Med only). Due to incomplete records, these four patients were not further analyzed.

Conditions and medications were compared across the three remaining groups (N= 125): (DX with Med n=36), (DX without Med n=23), and (No Dx and No Med n=66). There were no significant differences between the rates of psychiatric diagnoses or heart conditions. The (Dx without Med) group had a significantly higher rate of insomnia and obstructive sleep apnea (91%). Rates for painful conditions could not be compared because the category was too broad. There were no significant differences between the rates of prescribed antidepressants or heart medications. The (Dx without Med) group had a significantly higher rate of sleep aides (56%). The (No Dx and No Med) group had a significantly higher rate of narcotics (52%) compared to patients in both ADHD diagnosis groups.

Conclusions: Older adults have unique diagnostic challenges including but not limited to the following: 1) Missing childhood records, 2) Preexisting psychiatric, sleep, heart, pain or other conditions will influence scores on all self-assessment tools, 3) Patients may resist adjusting sleep or narcotic medications even if it improves their cognition, 4) Patients should expect several clinic visits to address all the diagnostic concerns including other referrals, and 5) Providers will be questioned about decisions to treat with stimulants, costs, delays in treatment and alternative therapies including hormones. Timely rigorous research is suggested to further define diagnostic challenges as well as treatment considerations for the older ADHD patient in primary care.

**F8. Clinical Correlates of Working Memory Deficits in Non-Referred Youth With and Without ADHD: A Controlled Study

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Background: Working memory (WM) refers to a key brain system that provides temporary storage and manipulation of information essential for adequate cognitive functioning. The extant literature documents that individuals with Attention Deficit Hyperactivity Disorder (ADHD) often have deficits in this area. A recent study found that referred youth with ADHD had significantly more WM deficits than controls. Additionally, WM deficits significantly and selectively increased the risk for academic deficits and cognitive dysfunction beyond those conferred by ADHD.
The main aim of the present study was to assess the clinical correlates of WM deficits in non-referred children by analyzing data from a large sample of non-referred siblings of probands with and without ADHD.

Methods: Participants were youth of both sexes derived from a longitudinal, case-control family study. This analysis relied on the non-referred biological siblings of these probands with and without ADHD.
Assessment included measures of psychiatric, psychosocial, educational, and cognitive functioning. WM was assessed through the Freedom from Distractibility (FFD) Factor from the Wechsler Intelligence Scale for Children-Revised (WISC-R). All analyses were performed using regression models with robust standard errors to account for the non-independence of the siblings using Stata.

Results: Comparisons were made between siblings with WM deficits (N = 474) and siblings without WM deficits (N = 85). The rate of WM deficits did not significantly differ between siblings of control and ADHD probands. However, the rate of WM deficits did significantly differ between siblings with ADHD and siblings without ADHD (29% vs. 12%, $\chi 2 = 14.10$, $p<0.001$). There was also a significant difference in the rate of ADHD in siblings with WM deficits compared to siblings without WM deficits (32% vs. 14%, $\chi 2 = 14.40$, $p<0.001$). Compared to siblings without WM deficits, siblings with WM deficits had significantly: higher rates of language disorders; more impaired DSM-IV Global Assessment of Functioning scores; more spare time problems on the Social Adjustment Inventory for Children and Adolescents; more impairment on the Child Behavior Checklist School Competence scale; lower scores on Wide Range Achievement Test Arithmetic and Reading; and higher rates of learning disabilities. Additionally, they were more likely to receive tutoring and be placed in special classes.

Conclusions: The present study extends the previous findings from referred youth with ADHD to non-referred siblings. The cognitive and academic burdens associated with WM deficits in the context of ADHD have clinical and scientific implications for children who have not been referred for neuropsychological evaluations. The presence of WM deficits significantly taxes the already compromised academic performance of ADHD children beyond that conferred by ADHD itself. Considering that WM deficits can only be documented through psychological testing, screening for such deficits can help identify a subgroup of ADHD children at very high risk for academic failure. Since pharmacotherapy for ADHD has a limited impact on WM deficits, identifying these children can help with the implementation of appropriate educational interventions. Scientifically, children with ADHD and WM deficits may represent a meaningful subgroup of ADHD children with unique neurobiological underpinning worthy of further investigation.

**F9. Examining the Association Between Attention Deficit Hyperactivity Disorder and Substance Use Disorders: A Familial Risk Analysis

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Background: The main aim of this study was to use familial risk analysis to examine the association between attention deficit hyperactivity disorder (ADHD) and substance use disorders (SUDs) attending to sex effects and the specificity of alcohol and drug use disorder risks.
Methods: Subjects were derived from two longitudinal case-control family studies of probands aged 6 to 17 years with and without DSM-III-R ADHD of both sexes and their first degree relatives (parents and siblings) followed from childhood onto young adult years. Cox proportional hazard models were used to estimate rates of ADHD and SUDs (any SUD, alcohol dependence, and drug dependence). Logistic regression was used to test both co-segregation and assortative mating.
Results: Our sample included 404 probands (ADHD: 112 boys and 96 girls; Control: 105 boys and 91 girls) and their 1,336 relatives. SUDs in probands increased the risk for SUDs in relatives irrespective of ADHD status. The risk for dependence to drug or alcohol in relatives was non-specific. There was evidence that even in the absence of a SUD in the proband, ADHD by itself increased the risk of SUDs in relatives. Proband sex did not moderate the familial relationship between ADHD and SUDs. There was evidence of co-segregation between ADHD and SUD.
Conclusions: Findings indicate that various independent pathways are involved in the transmission of SUD in ADHD and that these risks were not moderated by proband sex. ADHD children and siblings should benefit from preventive and early intervention strategies to decrease their elevated risk for developing a SUD.

**F10. Abnormal Fear Circuitry in ADHD: A Controlled Magnetic Resonance Imaging Study

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Background: Attention Deficit/Hyperactivity Disorder (ADHD) is a common, early onset, treatable neurobiological disorder associated with high morbidity and dysfunction. A recent meta-analysis documented a robust and bidirectional association between ADHD and PTSD in both referred and non-referred samples of adults and children. Because the onset of ADHD was consistently earlier than the onset of PTSD in all studies examining temporality, we hypothesized that ADHD may be an antecedent risk factor for PTSD and thus associated with a neurobiological vulnerability for PTSD.

The goal of this study was to examine whether individuals with ADHD have abnormalities in fear circuitry resembling those found in PTSD. We studied medication naïve young adults with and without ADHD with no history of trauma exposure using a validated fear conditioning and extinction neuroimaging paradigm. We hypothesized that non-traumatized, medication-naïve subjects with ADHD would demonstrate dysfunctional activation in brain structures that

mediate fear extinction and learning, consistent with those previously reported in subjects with PTSD.

Methods: A total of 27 (13 male and 14 female) non-traumatized, right-handed, medication-naïve, young adult subjects age 19-33 (M = 23, SEM = 1) with ADHD were compared to 20 (10 male and 10 female) non-traumatized, right-handed healthy controls (HC) age 21-34 (M = 26, SEM = 1). ADHD subjects were recruited from referrals to an adult ADHD program at Massachusetts General Hospital and through media advertisements. Controls were recruited from the community and free of current psychiatric disorders. All ADHD subjects were diagnosed with childhood-onset and persistent DSM-IV-TR.

Participants underwent a 2-day fear conditioning and extinction paradigm in a 3-T fMRI scanner. The protocol was identical to one previously developed and validated in healthy subjects and clinical populations including PTSD, OCD, and schizophrenia. Conditioning and extinction training were conducted on day 1. Extinction recall was conducted on day 2. Skin conductance response (SCR) was obtained as an index of the conditioned response.

Results: Compared to healthy controls, ADHD subjects had significantly greater insular cortex activation during early extinction, lesser dorsal anterior cingulate cortex (dACC) activation during late extinction, lesser activation in ventromedial prefrontal cortex (vmPFC) during late extinction learning and extinction recall, and lesser activation in hippocampus during extinction recall. Hippocampal and vmPFC deficits were similar to those documented in PTSD subjects compared to traumatized controls without PTSD.

Conclusions: Non-traumatized, medication naive adults with ADHD had abnormalities in fear circuits during extinction learning and extinction recall consistent with those previously documented in subjects with PTSD compared to traumatized controls without PTSD. These findings, if confirmed in future studies, would support the hypothesis of a neurobiological vulnerability to PTSD in ADHD and help explain the significant association between ADHD and PTSD.

F11. Impaired Frontal-Limbic White Matter Maturation in Children at Risk for Major Depression

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Background: Depression is among the most common neuropsychiatric disorders. It remains unclear whether brain abnormalities associated with depression reflect the pathological state of the disease or neurobiological traits predisposing individuals to depression. Parental history of depression is a risk factor that more than triples the risk of depression.
Methods: We compared white matter microstructure cross-sectionally in 40 children ages 8-14 with versus without parental history of depression (At-Risk vs. Control). Twenty offspring (ages 8 – 14) of parents with lifetime history of MDD (At-Risk group; mean age 11.1±1.57 years) and 20 age-matched offspring of parents with no lifetime MDD (Control group; mean age 10.65±2.12 years) participated in this study.
Results: There were significant differences in age-related changes of fractional anisotropy (FA) between the groups, localized in the anterior fronto-limbic white matter pathways, including the anterior cingulum and the genu of the corpus callosum. Control children exhibited typically increasing FA with age, whereas At-Risk children exhibited atypically decreasing FA with age in these fronto-limbic regions. Furthermore, dorsal cingulate FA significantly correlated with depressive symptoms for At-Risk children.
Conclusions: The results suggest maturational white matter microstructure differences in mood-regulatory neurocircuitry that may contribute to neurodevelopmental risk for depression. The study provides new insights into neurodevelopmental susceptibility to depression and related disabilities that may promote early preventive intervention approaches.

**F12. Nicotine-Induced Epigenetic Modification of Male Germline DNA is Associated With ADHD Phenotypes in the Offspring

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Background: Cigarette smoking and other forms of tobacco use remain leading causes of disease, disability and death in the United States. Another public health concern is the link between cigarette smoking and ADHD, as well as cigarette smoking by women during pregnancy. The latter is known to nearly double the risk for ADHD in the children. Although cigarette smoking by pregnant women remains a major concern, a greater proportion of men smoke cigarettes than women. Yet, whether tobacco use by men can produce adverse impact on the offspring – other than via second hand cigarette smoke exposure – is not known.
Methods: Since environment-induced epigenetic modification of germ cell DNA can transmit behavioral phenotypes to future generations, and since nicotine can produce epigenetic modification of DNA, two intriguing questions arise: Can nicotine produce epigenetic modification of germ cells, and if so, could such epigenetic modifications be the basis for transmission of cognitive phenotypes to the offspring (next generation)? To address these intriguing questions, we developed a paternal nicotine exposure mouse model in which adult male mice were exposed to nicotine (200µg/ml) in drinking water for 12 weeks. While the nicotine

exposure was ongoing, the mice were bred with drug naïve females. To evaluate the hypothesis that nicotine can induce epigenetic modification of male germ cell DNA, we collected spermatozoa from the nicotine exposed males and examined methylation of spermatozal DNA using DNA immunoprecipitation combined with qPCR.
Results: We found significant changes in genome-wide DNA methylation as well as DNA methylation at dopamine receptor promoter regions in the nicotine-exposed fathers' spermatozoa. The offspring of the nicotine-exposed males displayed hyperactivity and inattention, phenotypes commonly associated with ADHD. Interestingly, the nicotine-exposed mice (fathers) did not display either of these behavioral phenotypes. We also examined dopamine receptor mRNA expression in the offspring's brain using quantitative real-time PCR. Dopamine D1, D2, D4 and D5 receptor mRNA showed sex- and brain region-specific changes in the offspring, although the offspring were not exposed to nicotine during their life cycle.
Conclusions: These data suggest that nicotine-induced epigenetic modification of the father's germ line is associated with behavioral phenotypes and molecular changes in the offspring's brain. Our findings call for revision of the current education, research and public health efforts, which focus primarily on nicotine exposure of women, so that nicotine's effects on men, especially their germ line, can receive equal attention.

**F13. Reduced Subcortical Volumes in Preschoolers With ADHD

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Background: Anomalous brain structure and function is implicated in children with attention-deficit/hyperactivity disorder (ADHD). However, most neuroimaging research has examined school-aged children, despite the typical onset of symptoms in early childhood. This study examined whether the volume of subcortical structures, including the basal ganglia (caudate, putamen, and globus pallidus) and thalamus, differ among preschoolers with ADHD in comparison to typically developing (TD) children.
Methods: High resolution T1-weighted 3D MPRAGE images covering the whole brain were acquired on a 3T scanner and subcortical volumes were automatically extracted. Analyses were conducted in a total of 91 medication-naïve preschoolers, ages 4-5 (51 with ADHD, 40 controls; 63% boys). ADHD was diagnosed using modified DSM-IV criteria based on a structured psychiatric interview and caregiver ratings. Group differences (ADHD vs. TD) in subcortical volumes (normalized to account for differences in total cerebral volume) were examined using multiple univariate ANOVAs with a false discovery rate (FDR) correction applied. Cohen's d was also calculated as an estimate of effect size.
Results: Results revealed reduced generally reduced subcortical volumes in preschoolers with ADHD. The largest reductions were observed for the left caudate ($p = .012$, $d = .54$) and the left thalamus ($p = .007$, $d = .58$), with small to moderate non-significant reductions in the remaining subcortical structures (ds ranging from .22 to .40).
Conclusions: These findings suggest that subcortical volumes are reduced among preschoolers with ADHD with the greatest reductions seen in the left caudate and thalamus. Consideration of these findings in relation to our previous study reporting that subcortical volume reductions were greatest in the globus pallidus and putamen among school-aged children suggests that subcortical

anomalies in children with ADHD may shift early in development. Longitudinal research is needed to clarify these cross-sectional findings.

F14. Intrinsic Functional Connectivity of Approach and Avoidance Circuitry in ADHD

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Background: Fundamental alterations in basic reinforcement and motivational processes have been postulated as crucial to causation as well as intervention for attention-deficit/hyperactivity disorder (ADHD). Despite the extant literature examining motivational deficits in ADHD, it remains unclear whether ADHD is characterized by atypical approach or avoidance motivation and associated disruptions in the related neural circuitry. This study compared intrinsic functional connectivity of prefrontal cortex (PFC) with the striatum (involved in approach motivation) and amygdala (involved in avoidance motivation) in children with and without ADHD without any comorbid disorders.
Methods: We acquired resting-state functional magnetic resonance imaging scans from 82 8-12 year-old children (29 ADHD). Group independent component analysis was used to estimate functional connectivity between striatal-PFC regions and amygdala-PFC regions. Functional connectivity was compared between diagnostic groups (ADHD vs. TD) using ANCOVA with age as a covariate.
Results: Results suggest that striatal-PFC regions are intrinsically more out-of-sync in TD children (mean connectivity = -.076) compared to children with ADHD (mean connectivity = .039; p=.015, d=.58). Further, diagnostic groups did not differ in functional connectivity of amygdala-PFC regions (p=.644, d=.11).
Conclusions: These findings suggest atypical intrinsic functional connectivity of brain regions involved in approach motivation among children with ADHD. Perhaps greater synchrony between striatal-PFC regions contributes to heightened sensitivity to reward among children with ADHD and the associated behavioral manifestations. Our results also suggest similar amygdala-PFC connectivity, involved in avoidance motivation, among children with ADHD compared to TD controls. Future research examining motivational neural circuitry in children with ADHD and comorbid internalizing disorders may reveal disruptions in avoidance circuitry that were not seen in the current sample of children with ADHD without comorbid disorders.

F15. Abnormal Flow Patterns for Attention Deficit/Hyperactivity Disorder (ADHD)

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Background: ADHD is a condition that affects 6 million children in the US, and 5-7% of children worldwide (Gallo & Posner, 2016). These children present with symptoms of inattention, hyperactivity and impulsivity that interferes with academic and social functioning. Neuroimaging in children with ADHD has been used to suggest neurodevelopmental origin and areas of neuropathology. One of the easiest neuroimaging modalities to explore the neural underpinnings is the scanning of blood flow at rest. To date, there have been only a handful of such investigations

of ADHD (Kim et al., 2010; Kim, Lee, Shin, Cho, & Lee, 2002; O'Gorman et al., 2008), operating both with Single Photon Emission Computed Tomograph (SPECT) and Arterial Spin Labeling (ASL). While limited by low subject numbers and liberal thresholds for statistical inference, these studies suggest both decreased and increased blood flow in individuals with ADHD relative to healthy controls.

Our objective is to expand on prior work by conducting an ASL study with increased number of subjects, and utilizing both univariate and multivariate analyses. Multivariate analysis has not previously been used in ASL studies, and may be able to pinpoint blood flow patterns in ADHD.

Methods: Forty-eight participants were scanned, including 24 healthy control subjects (13M, 11 F, mean age 18.3 years, STD 4.4 years), and 24 participants with ADHD (18M, 6F, mean age: 12.3 years, STD: 5.6 years). Because of the difference in ages between healthy control and ADHD participants, we used subsamples that were group matched on age. Diagnoses were made using the Kiddie- Schedule for Affective disorders and Schizophrenia (K-SADS) and confirmed by a board-certified psychiatrist. ADHD participants were excluded if they were found to have a diagnosis of autism, bipolar disorder, psychotic disorder, or substance use disorder. Other comorbid disorders were recorded and covaried for subsequent analyses. Participants were also excluded if they had neurological illness, significant head trauma, serious medical problems, or MRI contraindications. All participants were scanned using an eight-channel brain array coil on a 3 Tesla (T) MRI GE scanner. 3D-PCASL perfusion imaging was performed in all participants using a fast-spin-echo stack-of-spiral readout module with 8 in-plane spiral interleaves.

Results: The univariate analysis of ADHD-related differences in the age matched subsample showed only regions with increased blood flow, with an uncorrected $p<0.001$. Overall, roughly 8% of all voxels showed a significant difference at the uncorrected p-level $p<0.001$, leading to an estimated false discovery rate of $0.001/0.08=1.25\%$. Increased blood flow was found primarily in the bilateral posterior perceptual and hippocampal regions, and in a large cluster of anterior cingulate cortex. No disease-related decreases in blood flow were found. Multivariate analyses suggested that ADHD participants do not manifest the age-related changes in blood flow observed in healthy controls.

Conclusions: Regions of disease-related increases in blood flow were located in the posterior hippocampus, and occipital and cingulate cortices. Future research will aim to extend these cross-sectional observations to longitudinal data and neuroimaging data of other modalities (resting state-fMRI) to elucidate mechanism and inter-modality relationships.

F16. Long Term Outcomes of Young Adults With 22q11DS and Comorbid ADHD

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Background: 22q11.2 deletion syndrome (22q11DS) is the most common identified microdeletion syndrome and is associated with a variety of health problems, developmental delays and psychiatric comorbidities. The current study focuses on ADHD in this population, as it is highly comorbid with 22q11DS. Despite the high rate of comorbidity between ADHD and 22q11DS there has previously been very little longitudinal work done on this population. The only previous study to investigate this topic, a previous three-year longitudinal study of ADHD into early adolescence in 22q11DS, provided evidence that childhood factors that predict ADHD

persistence in non-22q11DS populations also predict persistence in individuals with 22q11DS. Further investigation of predictive factors and functional consequences in later adolescence and young adulthood is necessary to understand and ultimately reduce the risk of ADHD's negative impact in the 22q11DS population. The current study represents a 9-year longitudinal study investigating the course of ADHD in 22q11DS from late childhood through young adulthood. Our analyses focused on (a) describing the developmental trajectory of ADHD and associated functional impairments in 22q11DS and (b) assessing ADHD outcomes from both a categorical and dimensional perspective.

Methods: Children with 22q11DS with (n = 37) and without ADHD (n = 35) were followed from ages 12 to 21. Participants were comprehensively assessed with structured diagnostic interviews and assessments of behavioral, cognitive, social, school, and family functioning at 4 time points (every 3 years). Control participants both with and without ADHD were also followed prospectively.

Results: An ADHD diagnosis in childhood predicts to functional impairments in multiple domains in 22q11DS, at levels greater than observed in our control participants with ADHD. Similarly, from a dimensional perspective, elevated levels of inattention and hyperactivity-impulsivity predict to functional impairments in 22q11DS. These results have implications for understanding how ADHD presents in a population with developmental delays.

Conclusions: The current study examined the longitudinal trajectories of individuals with comorbid 22q11DS and ADHD. This is the first study to examine outcomes and the impact of ADHD in young adulthood for individuals with 22q11DS. Future research should focus on the impact of evidence-based treatments for ADHD in this population to help mitigate the negative outcomes associated with ADHD in adulthood in 22q11DS.

F17. Factors Associated With Parental Evidence-Based Treatment-Seeking for Childhood ADHD

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Background: Childhood ADHD is a clinically significant and impairing mental illness with long-term negative outcomes in a variety of domains (Barkley, Fischer, Smallish, & Fletcher, 2006; Kessler et al., 2005; Molina et al., 2009). Despite this, there is a significant delay to treatment and a low rate of lifetime treatment contact for individuals with ADHD (Wang et al., 2005). Barriers to treatment include poor symptom recognition, attitudinal barriers, evaluative barriers, fear of stigma, and structural barriers (Bussing, Zima, Gary, & Garvan, 2003; Mojtabau et al, 2011; Sayal, Goodman, & Ford, 2006). These barriers are important to consider in the context of the family system as parents serve as gatekeepers to mental health treatment for their children. In addition, parents' perceptions of the quality and type of their children's symptoms may also inform their treatment making decisions (Sayal et al., 2006). Our study aims to examine (a) predictors of treatment-seeking attitudes, (b) predictors of information-seeking behaviors, and (c) the relationship between treatment-seeking attitudes and information-seeking behaviors in a pre- and non-treatment-seeking parent population (i.e., a population of parents who have not sought treatment for ADHD).

Methods: We collected data from 102 parents of children in the United States. This was a sample of parents whose child was not involved in any ADHD treatment, both historically and currently.

Participants completed an online study that assessed their perceptions of their own children's symptoms, parenting self-efficacy, potential misconceptions about ADHD treatment, mental illness history for parent and child, medication experience for parent and child, knowledge about mental illness, symptom recognition, treatment attitudes, and information-seeking behavior.
Results: Multiple linear regressions were conducted using parents' perceptions of their children's ADHD symptoms, parenting self-efficacy, and misconceptions about ADHD treatment (Hypothesis 1a, 2a), mental illness and medication history of both parent and child (Hypothesis 1b, 2b), and knowledge about mental illness and symptom recognition (Hypothesis 1c, 2c) as possible predictors for treatment attitudes and information-seeking behavior. We also used a linear regression to examine using treatment attitudes as a predictor for information-seeking behavior (Hypothesis 3). Intriguing results regarding predictive factors of parental treatment-seeking for their children's ADHD symptoms emerged from the data.
Conclusions: Despite the negative consequences of untreated ADHD (Shaw et al., 2012) and the existence of effective treatment for ADHD (Pliszka, 2007), there is a significant delay to treatment contact for individuals with ADHD (Wang et al., 2005). The current study examined potential barriers to treatment for parents of children who have not sought treatment for ADHD. This is the first study to examine predicting factors of treatment-seeking in a non-treatment-seeking population regardless of ADHD symptomology. Given the high rates of untreated and undiagnosed ADHD, this population is of significant research importance. To the extent that barriers to treatment for these parents remain unaddressed, the effectiveness of our evidence-based treatments are decreased. Future research must focus on reducing these barriers and thus increasing access to evidence-based treatments and decreasing the long-term negative impacts of ADHD.

F18. An Open-Label Trial of N-Acetylcysteine in the Treatment of Pediatric Bipolar Spectrum Disorders: An Interim Analysis

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Background: Pediatric bipolar disorder is increasingly recognized as a prevalent and highly morbid disorder. The disorder is frequently treated with a multitude of medications despite a lack of efficacy and safety data (Biederman, J., et al., 1998). N-Acetylcysteine (NAC), a natural alternative to classic mood stabilizers, may offer a safe and healthful option for treating symptoms of bipolar disorder in youth. Previous research has demonstrated NAC's utility in the treatment of bipolar disorder in adults (Berk, et al., 2008; Berk et al., 2011). NAC's safety in pediatric populations has also been demonstrated (Ghanizadeh & Moghimi-Sarani, 2013; Hardan et al., 2012). While emerging research suggests that NAC may be an effective treatment for bipolar disorder, to our knowledge, there are no published data to date in the pediatric bipolar population, specifically. Subsequently, we completed an interim analysis of a 12-week, open-label trial to evaluate the efficacy and tolerability of NAC in children and adolescents 5-17 years old with bipolar spectrum disorder. We hypothesized that NAC would be effective in reducing symptoms of bipolar spectrum disorders and would be well tolerated. We report on the first 13 subjects in this interim analysis.

Methods: Participants were ages 5-17 meeting DSM-5 diagnostic criteria of a bipolar spectrum disorder (bipolar disorder- I, II, or Not Otherwise Specified (NOS), and displaying mixed, manic, or hypomanic symptoms (without psychotic features) at the time of evaluation. All subjects received open label treatment with BioAdvantex brand N-Acetylcysteine ("PharmaNAC"), which comes in 900mg tablets. All subjects began with a dose of 900mg in Week 1 of the trial, increasing to 1800mg per day in Week 2 (the maximum dose for subjects ages 5-12), and finally 2700mg in Weeks 3 and onward (for subjects ages 13-17 only). Severity of symptoms of mania was assessed weekly with the YMRS scale. Depression, ADHD, and psychotic symptoms were evaluated at baseline, midpoint and endpoint with the Children's Depression Rating Scale (CDRS), the Hamilton Depression Scale (HDRS), the ADHD Rating Scale, and the Brief Psychiatric Rating Scale (BPRS) respectively. To determine clinically significant severity and improvement relative to baseline, we used the NIMH Clinical Global Impression (CGI) severity (CGI-S) and improvement (CGI-I) scales. CGI severity and improvement were assessed separately for mania and depression. Safety was assessed at each visit using spontaneous reports of treatment-emergent adverse events. Changes in vital signs including blood pressure, temperature, height, and weight were recorded at every in-office visit. Response was defined as having either a 30% reduction in symptoms according to the YMRS at endpoint or by a rating of "much improved" or "very much improved" on the CGI-Improvement for mania ($\leq$2).
Results: The study population experienced decreases in average ratings, from baseline to end point, on all measurements used in the study: the YMRS, HDRS, BREIF, and the ADHD Rating Scale. The decrease in average YMRS ratings was statistically significant: change of -5.0 $\pm$ 5.7, p=0.02. Adverse events experienced by study participants were extremely limited.
Conclusions: The data suggests that NAC was effective in reducing manic and depressive symptoms in bipolar youth. Furthermore, the treatment was well tolerated. If similar results are found in larger studies, NAC could be considered an efficacious and safe alternative treatment for pediatric Bipolar Spectrum Disorders.

F19. Algorithm for Adult Attention Deficit Hyperactivity Disorder Management From the Psychopharmacology Algorithm Project at the Harvard South Shore Program

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Background: ADHD is a neurodevelopmental disorder with a worldwide rate of approximately 3-10% in school-age children. It often continues to show manifestations in adults, with up to 4% diagnosed adults worldwide. These patients suffer from a multitude of functional impairments with overall negative impacts on their quality of life.
Methods: A medication algorithm for adult ADHD was created using systematic literature search to identify relevant studies and key findings. We prioritized treatment considerations based on the following: 1) effectiveness and efficacy 2) Co-morbidity with other psychiatric or medical conditions 3) safety and long-term tolerability.
Results: After an accurate diagnosis of adult ADHD and after accounting for any comorbidity that may affect the algorithm, we propose initiating treatment with a low dose (5 mg) of methylphenidate (MPH) or amphetamine once daily and titrating the dose every 3 days until effectiveness occurs or until side effects develop, with the usual efficacious dose being 1-1.3 mg/kg for MPH and 0.6-0.9 mg/kg for amphetamines.

In adult ADHD and co-morbid substance use, we recommend deferring ADHD pharmacotherapy until a period of sobriety has been established, after which the first line medication would be atomoxetine at a target dose of 1.2 mg/kg. In patients who develop mania or psychotic symptoms while on stimulants, we recommend discontinuing stimulants and reconsidering your diagnosis. In patients with established bipolar disorder, we recommend stabilizing mood with mood stabilizers followed by a slow and careful addition of low dose stimulants along with close monitoring of symptoms as this patient population remains at a higher risk for developing mania.

Conclusions: This algorithm is supported by the available but limited latest evidence and was created in response to the growing need for a treatment guide to clinicians when choosing medications for Adult ADHD.

F20. Are Stimulants Useful in the Management of Mild Traumatic Brain Injury?

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Background: Mild traumatic brain injury (mTBI) makes up the overwhelming majority of traumatic brain injuries, with an estimated 600 cases per 100,000 person-years worldwide. Interest in this injury has heightened as mTBI effects people's ability to work and go to school. Among the most common difficulties that individuals with mTBI experience are cognitive difficulties including deficits in attention, concentration and distractibility. Because the symptoms are reminiscent of those associated with ADHD, stimulants could have a role in alleviating them. The main aim of this review was to evaluate the body of knowledge on the use of stimulants in mTBI across all ages.

Methods: We conducted a literature search using Ovidmedline and PubMed, pscyhINFO through Ovid, CINAHL, Embase, and Cochrane. We compiled broad search terms to capture the study population, mild traumatic brain injury, and treatment, stimulants. Search algorithm included: (brain concussion OR brain injury OR head injury) AND (amantadine OR amphetamine OR methylphenidate OR Ritalin OR Adderall OR dextroamphetamine OR Provigil OR central nervous system stimulant OR stimulant). Inclusion criteria included: (a) original research, (b) articles written in English, (c) differentiation of mild TBI from other severity of brain injury. Articles were excluded if they failed to (a) present original research, (b) use a stimulant medication, (c) distinguish mild TBI from other severity of brain injury, or if (d) studies were not in humans.

Results: There were 1,511 articles that met the initial search criteria and 63 articles meeting eligibility. Nine original research studies evaluated the use of stimulants in subjects with mTBI. Six studies were in adults and three in children. Two studies captured exclusively mild TBI while others studies included all TBI severity. Symptoms targeted with stimulants included post-concussive symptoms, executive function and other cognitive symptoms, depression, anxiety, PTSD, fatigue, daytime sleepiness, pain, and quality of life. One study had a primary target of attention. Sample sizes across all studies were small, ranging from 14-32 subjects, and only 3 studies were randomized trials while others were open label or retrospective analyses. Six studies used immediate release methylphenidate and three studies amantadine. Methylphenidate was associated with improvement in measures of attention, processing speed, reaction time, working memory, fatigue, depression, and PTSD. Amantadine was associated with improved reaction time

and verbal memory. One study excluded patients with ADHD but a diagnosis of ADHD was otherwise not assessed in any of the study populations. No studies evaluated the use of stimulants in the management of subjects with mTBI and co-morbid ADHD.
Conclusions: Our literature review identified nine small studies on the use of stimulants in mTBI cases relying on highly heterogeneous populations and pursuing widely heterogeneous targets. Studies of methylphenidate targeted cognitive deficits, depression, and fatigue showing some improvement in these symptoms. The benefits of amantadine are unclear. While stimulants are most effective in the management of ADHD, and ADHD has been shown to be overrepresented in mTBI, no study considered the diagnosis of ADHD either premorbidly or post concussively. This state of affairs calls for more robust research in this clearly neglected area of clinical and scientific inquiry.

F21. The Role of Hispanic Parents' Negative Perceptions Relating to ADHD Treatment Outcomes

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Background: Attention deficit/hyperactivity disorder (ADHD) has a poorer treatment prognosis in Hispanics when compared to Caucasian patients. The reasons for these disparities are numerous, such as difficulties in accessing health care among the Hispanic population. Another reason that has not received enough attention is Hispanic parents' misconceptions of stimulant treatment for ADHD. Inadequate adherence of Hispanic parents can be related to parental concerns about ADHD medication. Hispanic parents tend to prefer natural treatments over the use of conventional drugs. Predominantly, when it comes to mental health, they often think drugs are addictive and have serious side effects. Also, many Hispanic patients prefer self-treatment, such as folk use of medicine (curanderismo), or may be reluctant and ashamed to discuss behavioral issues with a healthcare provider. Often, a mother sees her child's problem as a regular issue rather than a diagnosis and does not see the need to seek medical attention. These misconceptions lead parents to be more resistant to prescribed ADHD medication or to administer the medication inconsistently, if at all.
Methods: This study will examine how parents' perceptions of stimulant treatment can have a negative impact on ADHD treatment. In order to better address resistance to stimulant medication, the clinician and physician as a team should discuss reasons behind such resistance and understand how these reasons might be related to Hispanic culture.
Results: Research suggests that in Hispanic culture, individuals need a high level of empathy and compassion from their physicians to feel comfortable and secure with the choice of treatment.
Conclusions: Findings in this study indicate that when parents receive psychoeducation and are treated by culturally sensitive healthcare providers, their adherence to treatment improves.

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F22. Preliminary Outcomes From an Innovative Community-Based Behavioral Health (BH) Program Serving Families Insured Through a Managed Medicaid Plan in Central Texas

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Background: Area pediatric providers report a lack of access to behavioral health (BH) services for their patients. A local payer identified high healthcare utilization in children with behavioral needs. Evidence-based research shows the traditional "in office" model to be ineffective at producing long-term improvement in children with behavioral complexity. The purpose of this program is to offer BH services in a nontraditional delivery model. A weekly evening program is delivered in a capitated payment model with a BH team led by a psychiatric nurse practitioner. The team includes social workers, community health workers, and interpreters. This family-centered program, Anchoring, offers 34 evidence-based bilingual sessions to promote positive parenting, relationships, academic success, and mindfulness.

Methods: Pediatric primary care providers and school resource counselors refer children 5-17 years of age the BH program. Inclusion criteria: having a behavior problem or mental health diagnosis, insured with sponsoring managed Medicaid plan, and commitment to participate in evening program offerings. Exclusion criteria: behaviors or diagnoses that preclude ability to work in group setting (autism spectrum disorders, aggression, or significant social interactional symptoms).

Baseline-screening instruments are administered to the children and parents. The children/ parents are seen by the psychiatric mental health nurse practitioner to develop an individual plan of care during the evening sessions.

Results: We assess the impacts of this program on a range of child and family outcomes. Validated screening instruments include PedsQL Family Impact Module (FIM) and Pediatric Symptom Checklist (PSC). Since its inception in July 2015, the program has maintained engagement on 132 children and 62 families. Mean baseline scores are as follows:

- PedsQL FIM: 70
- Parent reported PSC: Total, 49.7; Attention, 3.9; Internalizing,16.6; Externalizing, 4.7
- Child reported PSC: Total, 24.6; Attention, 4.3; Internalizing, 3.7; Externalizing, 3.5
- Medical management of 75 children
- Potential diversion of medication in 57 children

Conclusions: The Anchoring program begins with a family meal and ends with a family activity. In between, the participants break into age appropriate groups for sessions. Medication management is embedded as needed. Offering dinner and childcare reduces barriers to participation and promotes sustained engagement. Embedding medication management is an additional incentive to families for participation. This program allows therapeutic relationships to develop between the families and the BH team. Embedded special programs, in conjunction with

Anchoring, offer customized interventions for engaged participants (such as somatic experiencing for a cohort of trauma survivors, and NAMI Basics).
We present findings on engagement and medical management of children and/or parent in this innovative BH integrated care model in a Medicaid population.

F23. Impact on the Family Unit of Early Morning Functional Impairments in Stimulant-Treated Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

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Background: To assess the impact of early morning functional (EMF) impairments on the family unit (caregivers, spouse, and siblings) in stimulant-treated children/adolescents with attention-deficit/hyperactivity disorder (ADHD) compared with families of children without ADHD.
Methods: An online quantitative survey was conducted with parents (≥65%) and/or primary caregivers of children/adolescents (aged 6–17 years) with or without ADHD who: (1) were taking a stimulant as the primary ADHD medication, (2) had been taking a stable dose for ≥3 months prior to the survey, and (3) had ADHD symptoms during the Early Morning Routine (EMR)—from the moment the child awakens to the time they leave for school—rated as ≥2 on a 10-point severity scale, with 1 denoting "mild" and 10 denoting "severe". Eligible caregivers rated the severity and frequency in family dysfunction (caregiver, spouse/partner, siblings) resulting from their child's EMF impairments. The ADHD and non-ADHD samples were compared using logistic regression with ADHD status as the outcome and family impact measures as independent variables.
Results: There were 330 caregivers of children with ADHD who met the first 2 criteria above and 300 who met all inclusion criteria (91% of sample) and completed the survey. Fifty caregivers of children without ADHD also completed the survey. The mean severity of EMF impairments was significantly higher in families of children with ADHD compared with families of children without ADHD (6.2 vs. 1.5; $p<0.001$), as was the median number of school days per week that their child had EMF impairments (4 vs. 1 days/week; $p<0.001$). In the ADHD sample, the majority of caregivers reported their child's early morning ADHD symptoms (87%) and impairment of EMF (77%) as moderate to severe (rating of 5–10). Caregivers of children with ADHD also reported a significantly higher severity (up to 6-fold higher) and frequency (up to 9.5-fold higher) in family dysfunction on all measured domains during the EMR resulting from their child's inadequately controlled ADHD symptoms compared with caregivers of children without ADHD. Nearly half of the caregivers of children with ADHD expressed significantly higher concerns regarding the safety of their child and that of their siblings as a result of the EMF impairments related to the child with ADHD.
Conclusions: Compared with caregivers of youth without ADHD, primary caregivers of stimulant-treated children and adolescents with ADHD report a significantly higher prevalence and severity of EMF impairments. These impairments exert a pervasive and negative emotional and functional impact on the primary caregiver and on the entire family unit (i.e., spouse/partner and siblings).

F24. Short & Long-Term Impact of a Nutritional Approach on ADHD Management: A Real World Study

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Background: Today, there is growing scientific evidence supporting the association between Attention-Deficit Hyperactivity Disorder (ADHD) and lipid imbalances, thus lipid based therapies represent an important novel approach for managing ADHD behaviors in children.
PS-Omega-3 is a unique lipid composition available as prescription medical food for the dietary management of certain lipid imbalances associated with ADHD. Previously, in a double-blind placebo controlled clinical study, this composition was shown to significantly reduce ADHD behaviors, especially in children with emotional dysregulation. PS-Omega-3 was also shown to be safe and well tolerated in children.

In this study, the short & long term effects of PS-Omega-3 in a real-world setting was evaluated.

Methods: Between 2012 and 2016, 518 ADHD patients were identified through their electronic health records. The analysis was performed in two phases. The first phase evaluated the short term effect of PS-Omega-3 with an average administration of 6 months. The data collected in this short term phase included: demographics, concomitant medications, treatment duration, and self-rating of the treatment effect.
The second phase of the analysis evaluated the effect of PS-Omega-3 in a sub-cohort of 102 patients who consumed PS-Omega-3 for an average of 35 months. The effect of PS-Omega-3 was evaluated using the Clinical Global Impression of Change (CGIC), as well as by a self-rated outcome tool.

Results: 518 patients met the inclusion criteria for the study with a mean age of 11 years. Sixty-five percent of the patients were taking PS-Omega-3 concomitantly along with other ADHD prescription medications. Sixty eight percent of the patients reported an overall positive response to PS-Omega-3 over a short term administration period. Similar response rates were reported when PS-Omega-3 was used as an adjunct or mono therapy (66% & 73%, respectively). Interestingly, 31% out of the patients that reported a positive response were able to reduce their ADHD medication dosage following PS-Omega-3 administration.
In the second phase of the study, after an average of approximately 3 years follow up, the percent of patients judged as clinically improved (CGIC < 4) was 68%. In addition, 58% of the patients reported an improvement in their academic achievements, 47% in their social relationships, and 40% in their family life/functioning. Moreover, 45% of patients administered PS-Omega-3 adjunctively with ADHD medications, and that suffered from re-emergence of ADHD symptoms after the ADHD medication wear off, reported improvement in the rebounding effects.

Conclusions: Results show that in a real world setting 68% of patients who incorporated PS-Omega-3 into their ADHD management routine were judged as clinically improved following an average administration period of 35 months. In addition, patients reported improvements in areas related to their overall functioning, including academic performance. These results further corroborate the findings observed in the double blind study and suggest that this unique composition may serve as an effective method for the management ADHD.

****F25. Efficacy and Safety of HLD200 in Children With Attention-Deficit/Hyperactivity Disorder: Results: From a Pivotal Phase 3 Trial**

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Background: Evening-dosed HLD200 delays the initial release of methylphenidate by approximately 8-10 hours, targeting the onset of clinically meaningful treatment effect upon awakening and lasting to the evening. The objective was to determine whether HLD200 improves control of ADHD symptoms, and at-home early morning and evening functional impairments versus placebo in children with attention-deficit/hyperactivity disorder (ADHD). Safety and tolerability were also assessed.

Methods: This was a pivotal, randomized, double-blind, multicenter, placebo-controlled, parallel-group, phase 3 trial of HLD200 in children (6-12 years) with ADHD (NCT02520388). Subjects had current or prior response on methylphenidate. Following a screening period of ≤2 weeks with a 3- to 7-day washout, subjects were randomized (1:1) to HLD200 or placebo once-daily each evening for 3 weeks. After 1 week, the initial 40 mg dose of HLD200 was titrated in 20-mg weekly increments to 60 mg and 80 mg, as tolerated, with a one-step down-titration permitted. The primary efficacy measure was the ADHD Rating Scale (ADHD-RS-IV) Total Score following 3 weeks of treatment. The key secondary efficacy measures were the Before School Functioning Questionnaire (BSFQ) and Parent Rating of Evening and Morning Behavior-Revised, Morning (PREMB-R AM) and Evening (PREMB-R PM) subscales following 3 weeks of treatment. Safety measures included treatment-emergent adverse events (TEAEs), with a focus on sleep and appetite.

Results: Of 163 children enrolled across 22 sites, 161 were included in the intent-to-treat population. After 3 weeks of treatment, children on HLD200 achieved a significant improvement versus those on placebo in ADHD symptoms (least-squares [LS] mean ADHD-RS-IV: 24.1 vs 31.2; P=0.002), at-home early morning functioning (LS mean BSFQ: 18.7 vs 28.4; P<0.001; LS mean PREMB-R AM: 2.1 vs 3.6; P<0.001), and at-home evening functioning (LS mean PREMB-R PM: 9.4 vs 12.2; P=0.002). No serious TEAEs were reported, and only 1 subject on HLD200 (1.2%) and 4 subjects on placebo (5.0%) had TEAEs leading to early withdrawal. The most common TEAEs (≥10%) reported by children on HLD200 were decreased appetite, and initial, middle, and terminal insomnia. Most sleep-related TEAEs were transient (ie, 96.6% resolved) and all were mild or moderate in severity.

Conclusions: Following daily evening administration, HLD200 was well tolerated and demonstrated significant improvements in ADHD symptoms and both at-home early morning and evening functional impairments versus placebo in children with ADHD.

****F26. DAT Occupancy Following Dasotraline Administration in Healthy Adult Subjects**

Seth Hopkins*[1], Robert Lew[1], Georges El Fakhri[2], Marc Normandin[2], Anna Hall[2], Barbara Storch[2], Jennifer Wicks[2], Dustin Wooten[2], Kira Grogg[2], Kenneth Koblan[1], Thomas Spencer[2]

[1]Sunovion Pharmaceuticals Inc., [2]Massachusetts General Hospital

Background: Dasotraline is a novel and potent inhibitor of human dopamine transporters (DAT; dopamine uptake IC50 3 nM) and norepinephrine transporters (NET; norepinephrine uptake IC50 4 nM), and is currently being investigated to evaluate its use in treating the symptoms of ADHD and in binge eating disorder (BED). The pharmacokinetic profile of dasotraline in adults is characterized by slow absorption and slow elimination, such that multiple daily doses are required to support accumulation to steady-state plasma concentrations, which remain stable over the dosing interval (Hopkins et al, Clin Drug Investig 2016). Clinical efficacy of methylphenidate in ADHD occurs with DAT occupancy of ≥50% and is achieved within each dosing interval (Volkow et al, Am J Psychiatry 1998). In contrast, clinical efficacy of dasotraline would be expected during relatively stable DAT occupancies that are maintained over the course of the dosing interval. This study (SEP-360-108) was designed to determine the onset of brain DAT occupancy and pharmacokinetics of dasotraline in healthy adults. Here, we report preliminary data on DAT occupancy over 7 daily doses of dasotraline in healthy adult subjects.
Methods: Prior to drug treatment, MRI scans (3T) were performed on each subject (N=5) for anatomical co-registration with subsequent functional PET images. Baseline PET scans with 11C-Altropane (~4 mCi) were also performed prior to dasotraline to measure binding activity to DAT in striatal regions. 11C-Altropane PET imaging scans were performed after dasotraline treatment (8 mg once daily) on Days 1, 2, 4, and 7 for each PET scan session. Plasma samples were taken prior to each PET scan to correlate % DAT occupancy with plasma levels of dasotraline. 11C-Altropane was injected intravenously over 30 seconds and serial PET images were acquired over 60 minutes. Following image reconstruction, PET analysis was performed using the Simplified Tissue Reference model with the cerebellum which is devoid of DAT as the reference region and DAT occupancy was determined.
Results: Median time to onset of 50% DAT occupancy was between days 2 and 3. Plasma-occupancy relationships within each subject determined that the average plasma concentration corresponding to 50% DAT occupancy (ED50) of dasotraline was 6 ng/mL; similar to the value reported in a prior PET study (DeLorenzo et al, J Nucl Med 2011) and to the value reported for methylphenidate in the literature. Increased heart rate was observed in all subjects, insomnia in 4 of 5 subjects, and palpitations/anxiety in 1 subject who discontinued study drug.
Conclusions: In healthy adults, daily doses of dasotraline 8 mg achieved the >50% DAT occupancy level expected for pharmacological effects before steady-state plasma concentrations had been reached. The safety profile was consistent with the known effects of DAT/NET inhibition. Implications for the proposed clinical use of dasotraline will be discussed.

**F27. Metadoxine Selectively Reverses Tonic and Phasic GABAergic Transmission Deficits in the FMR1 Mouse Model

Johanna Schumann[1], Jonathan Rubin*[1], Yaron Daniely[1], Amit Modgil[2], Moss Stephen[2]

[1]Alcobra, Inc., [2]Tufts University School of Medicine

Background: Coordination of synaptic transmission depends on an adequate balance of excitation and inhibition, modulated, in part, by GABAergic inhibitory transmission. Phasic inhibition is mediated by synaptic low-affinity GABA receptors resulting in a rapid, transient GABAergic conductance. Tonic inhibition is mediated by high-affinity extrasynaptic receptors resulting in

persistent GABAergic conductance. Alteration in tonic inhibition has recently received significant attention as a mechanism underlying the pathophysiology of various CNS disorders. Attention Deficit Hyperactivity Disorder (ADHD) is associated with a deficit in cortical inhibition via the GABAergic system and reduced GABA levels in children with ADHD. Evidence for reduced tonic levels of GABA in the hippocampus of a validated animal model of ADHD, the spontaneously hypertensive rat, was also demonstrated. Excitatory/inhibitory synaptic transmission imbalance has been reported in animal models and patients with Fragile X Syndrome (FXS). Indeed, tonic inhibition in hippocampal subicular neurons and tonic and phasic inhibitory currents in the amygdala were found to be significantly reduced in knock-out (KO) mice1.
Metadoxine Extended Release (MDX) is under development for the treatment of ADHD and FXS. Our previous data indicate a novel monoamine-independent mechanism of action of metadoxine, characterized by GABAergic transmission modulation. To further elucidate the mechanism of action of metadoxine, we investigated its electrophysiological effects on phasic and tonic inhibition in hippocampal dentate gyrus granule cells (DGGC) of wild-type (WT) and Fmr1 KO mice (a murine model of FXS).

Methods: Tonic and phasic GABA currents were recorded by whole-cell patch-clamp from hippocampal DGGC slices (35 micron) from p21-35 WT C57, or Fmr1 KO mice. Tonic current was determined by measuring the difference in holding current amplitude before and after applying 100 μM picrotoxin and in the presence of 1 μM GABA. Amplitude, frequency and decay time of phasic spontaneous inhibitory postsynaptic currents (sIPSCs) were analyzed using Minianalysis software (Synaptosoft). The effects of metadoxine on tonic and phasic currents were evaluated at 300 and 450 μM.
Results: Untreated slices from Fmr1 KO mice exhibited a significant reduction in tonic current amplitude and density compared to age-matched WT control mice, while direct application of metadoxine (450 μM) significantly increased current amplitude and density in KO slices as compared to untreated KO slices, indicating reversal of tonic current deficits in Fmr1 KO mice. Metadoxine did not show any effect on WT control slices. Fmr1 KO mice also displayed larger sIPSCs amplitude compared to control. Metadoxine (450 μM) normalized GABAergic phasic inhibition deficits, while it did not affect sIPSC amplitude in WT slices.
Conclusions: These findings expand our previous data indicating a novel mechanism of action of metadoxine, characterized by GABAergic transmission modulation and demonstrate that metadoxine reverses hippocampal GABA tonic and phasic inhibition deficits seen in a mouse model of FXS. As dysregulation of tonic current has been established in both ADHD and FXS, normalization of these deficits may be part of the mechanism by which metadoxine improves clinical symptoms in these cognitive disorders.

F28. OPEN BOARD

F29. Dasotraline Enters the Brain More Slowly Than Methylphenidate in Rhesus Monkeys

Robert Lew*[1], Cristian Constantinescu[2], Vincent Carroll[2], Olivier Barret[2], Kenneth Koblan[1], Seth Hopkins[1]

[1]Sunovion Pharmaceuticals Inc., [2]Molecular NeuroImaging, a division of InviCRO

Background: Drugs that increase dopamine levels may be associated with stimulant effects and abuse. Faster onset kinetics is associated with greater drug liking. Slowing the rate of increase in brain dopamine transporter occupancy decreases drug liking of methylphenidate (Spencer et al, Am J Psychiatry 2006). Dasotraline, a novel and potent inhibitor of human dopamine transporters (DAT; dopamine uptake IC50 3 nM) and norepinephrine transporters (NET; norepinephrine uptake IC50 4 nM), is currently being investigated to evaluate its use in treating the symptoms of ADHD and in binge eating disorder (BED). Dasotraline, when taken orally, demonstrates pharmacokinetics characterized by slow absorption and slow elimination (Hopkins et al, Clin Drug Investig 2016). Dasotraline exhibits a low potential for abuse, possibly related to its slow absorption kinetics following oral doses (Koblan et al, Drug Alcohol Depend 2016). However, it remains unclear whether alternative routes of dasotraline administration would facilitate the rapid elevation of dopamine levels associated with stimulant drugs. This study compared the rate of brain entry for dasotraline vs methylphenidate following IV administration in rhesus monkeys.
Methods: The DAT PET radiotracer [18F]FE-PE2I was administered to rhesus monkeys (n = 3) via bolus plus constant infusion (B\I; 162 ± 27 MBq) for 4 hours to establish steady-state DAT binding. Two hours following administration of the radiotracer in each monkey, either dasotraline (0.1 and 0.2 mg/kg) or methylphenidate (0.1 and 0.5 mg/kg) was administered via IV administration (3-minute bolus). Reductions in tracer binding over time induced by dasotraline or methylphenidate were used to estimate brain entry rates. The [18F]FE-PE2I activity time curves in the putamen and caudate nucleus were fitted to a generalized reference tissue model (GRTM; Votaw et al, Synapse 2002) using the cerebellum as reference region. The tracer-binding state from the first pre-displacement steady state to the second post-displacement steady state was modeled as a time-varying decreasing exponential whose half-life represents the rate of brain entry of the drug. The maximum occupancy was constrained to the measured displacement, while the reference tissue tracer efflux rate constant, $k2'$, and the brain entry half-life was constrained to a common value across the putamen and caudate nucleus.
Results: Plasma concentrations of each drug demonstrated comparable kinetic profiles during the onset of DAT occupancy. Dasotraline achieved final level of occupancies of 52% (0.1 mg/kg) and 66% (0.2 mg/kg), while methylphenidate achieved occupancies of 73% (0.1 mg/kg) and 88% (0.5 mg/kg). The mean (±SD) estimated brain entry rates of dasotraline were 23.0 ± 4.9 minutes at 0.1 mg/kg and 14.7 ± 2.6 minutes at 0.2 mg/kg. For methylphenidate, the mean brain entry rates were 2.8 ± 0.1 minutes at 0.1 mg/kg and 2.5 ± 0.7 minutes at 0.5 mg/kg. These results indicate that the brain entry rates of dasotraline were approximately 6 to 8 times slower than the brain entry rates of methylphenidate.
Conclusions: In rhesus monkeys, the brain entry kinetics of dasotraline are slow relative to methylphenidate. Differences in the pharmacokinetics of the distribution at DAT sites may underlie the absence of abuse potential thus far associated with oral dasotraline administration. Future work will assess the effect of slow brain entry on dopamine kinetics at a synaptic level using 11C-raclopride, a dopamine receptor antagonist PET radiotracer.

Saturday Poster Abstracts

Saturday Poster Session
11:30 AM – 1:00 PM
East & State Ballroom

**S1. Relationship Between the WRAADDS Symptom Rating of Inattention in Adults With ADHD and Performance in CDR Cognitive Tests in a Clinical Trial Population

Seth Hopkins*[1], Robert Goldman[1], Antony Loebel[1], Kenneth Koblan[1]

[1]Sunovion Pharmaceuticals Inc.

Background: Inattentiveness is a core symptom of ADHD. To date, few studies have evaluated the relationship between clinical ratings of inattentiveness and cognitive performance of attention. Here we report the results from a post-hoc analysis examining the relationship between symptoms of inattention and the cognitive domain of attention in adults with ADHD.
Methods: Baseline data (prior to administration of study drug) were used from a 4-week study evaluating the efficacy and safety of dasotraline in 341 adult outpatients with a primary diagnosis of ADHD based on DSM-4 criteria (NCT01692782; SEP306-201; Koblan et al. Neuropsychopharmacology 2015). Symptoms of inattention assessed with the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) were compared to cognitive performance via the Cognitive Drug Research (CDR) computerized assessment. The WRAADDS subscore of Attentional Difficulties was the sum of ratings for: short attention span, distractibility, difficulty in listening, listening when in audience, attention when reading, and attentional difficulties summary rating. The CDR Power of Attention domain was the sum of: simple reaction time, choice reaction time, and digit vigilance. An exponentially modified Gaussian distribution function (ex-Gaussian parameters of mean μ, SD σ, and exponential decay τ) was fit by nonlinear regression of frequency distributions of Power of Attention. To evaluate the strength of association between the measures, Pearson correlation coefficients were calculated.
Results: The mean (SD) baseline WRAADDS total score was 35 (7.7) and Attentional Difficulties subscore was 12 (1.8). CDR power of attention scores exhibited an ex-Gaussian distribution (μ = 1135 ms [95% CI: 1083, 1186], σ = 79 ms [95% CI: 61, 97], τ = 125 ms [95% CI: 86, 165]), indicative of lapses in attention during the tasks. Patients with relatively fast Power of Attention (performance of less than μ = 1135 ms) had mean Attentional Difficulties scores between 11 and 12 points, whereas patients distributed in the exponential decay portion of the population distribution ($\mu + \tau$ = 1214 ms) had mean Attentional Difficulties scores between 12 and 13 points. Overall correlations between all cognitive domains and symptom domains were low ($r < 0.2$); however, greater cognitive lapses in attention were evident in patients with more severe attentional difficulty ratings ($r = 0.15$). No consistent relationship was observed in the distribution of performance between the CDR Power of Attention domain and any of the remaining 6 WRAADDS symptom domains or the total score.
Conclusions: The contribution of exponential processes to reaction times was indicative of delayed cognitive processes, or lapses in attention, contributing to increased reaction times across

the population. Patients performing with faster reaction times had lower ratings of inattention, despite the overall low correlation between symptom severity and cognitive performance. Nevertheless, the contribution of lapses in attention to the severity of inattentive symptoms appeared to be specific relative to other symptom vs cognitive domain comparisons, encouraging efforts to connect specific clinical symptoms with neurobiological processes in adults with ADHD.

S2. The Concurrent Validity of the Barkley Functional Impairment Scale in Mothers With ADHD

Tyler Sasser*[1], Mark Stein[2]

[1]Seattle Children's Hospital, [2]University of Washington

Background: Adults with ADHD demonstrate persistent functional impairments in social, educational, occupational, and financial domains (Barkley, 2014). Functional impairments are necessary requirements for the disorder and essential for identifying treatment targets and evaluating outcomes (Ramsay, 2014). The Barkley Functional Impairment Scale (BFIS; 2011) is an easy-to-administer 15-item, norm-referenced measure of functioning in adults that can be adopted in clinical and research settings. The BFIS forms a Total score, as well as a score reflecting the percent of domains (i.e., items) in which the individual is impaired. We sought to describe the degree and types of impairment in sample of multiplex families of mothers with ADHD who have young children with ADHD symptoms, and to examine the concurrent validity of the BFIS by examining its association with ADHD and mood symptoms, as well as other measures if impairment.

Methods: Study participants included 35 mothers with ADHD (mean age = 39.36 years, 89% Caucasian) who were participating a larger treatment trial and who also had a child (mean age 5.9) with elevated ADHD symptoms. Mothers and a significant other completed the BFIS-Self and BFIS-Other forms, respectively. Mothers also completed a measure of ADHD symptoms (the Conners Adult ADHD Rating Scale [CAARS]), depression (the Beck Depression Inventory [BDI]), and relationship (the Dyadic Adjustment Scale [DAS]) scales. Clinicians completed ratings of ADHD and mood symptoms (the Wender Reimherr Adult Attention Deficit Disorder Scale[WRAADDS]) and ADHD severity (Clinician Global Impressions Scale [CGI]).

Results: Mothers with ADHD reported clinically significant inattention symptoms on the CAARS (average T-score = 73.85), mild depression symptoms on the BDI (average total score = 16.47), and elevated impairment on the BFIS (average Total Score = 4.43; average percent of domains impaired = 43%, 89-90th percentile). Overall impairment on the BFIS-Self was significantly associated with just two of the 13 scales: the inattention scale of the CAARS ($r = .52$, $p < .01$) and overall score on the BDI ($r = .31$, $p < .05$). The percent of domains impaired on the BFIS-Self was significantly associated with the overall ADHD scale of the CAARS ($r = .37$, $p < .05$), the BDI ($r = .43$, $p < .05$), and the temper ($r = .45$, $p < .01$) and emotional over-reactivity ($r = .48$, $p < .01$) subscales of the WRAADDS. The overall impairment and percent of domains impaired on the BFIS-Other were significantly negatively correlated with the overall relationship adjustment rating on the DAS ($r = -.44$, $p < .05$ and $r = -.48$, $p < .05$, respectively), but no other scales.

Conclusions: Mother self-rated impairment was associated with ADHD symptoms to a modest degree, but not with clinician-rated ADHD symptoms and severity. Interestingly, according to clinician ratings, mood symptoms were more consistently associated with functional impairments than were ADHD symptoms or severity. Although the BFIS-Other was not significantly associated

with mother- or clinician-rated ADHD or mood symptoms, there was evidence of convergence with mother ratings of relationship adjustment. Considered together, these findings suggest that impairment and mood symptoms should be tracked as well as ADHD symptoms, and that mothers with ADHD with young children with ADHD display a wide range of impairments that may require comprehensive treatment programs that extend beyond symptom control, and may include CBT, couples therapy, as well as pharmacotherapy.

S3. How Informative Are Self Reports of Adults With ADHD for Monitoring Treatment in the Clinical Setting?: A Pilot Report Examining the Correspondence Between Clinician and Patient Assessments

Maura Fitzgerald*[1], Joseph Biederman[2], Thomas J. Spencer[2], Lenard Adler[3], Jessica Abrams[1], K. Yvonne Woodworth[1], Stephen Faraone[4]

[1]Massachusetts General Hospital, [2]Massachusetts General Hospital & Harvard Medical School, [3]NYU School of Medicine, [4]SUNY Upstate Medical University

Background: ADHD is a neurobiological, prevalent and highly morbid disorder estimated to afflict at least 5% of adults in this country. While the validity of the diagnosis of adult ADHD has been recognized, questions remain as to whether adults with ADHD are good informants of their own symptoms. This issue becomes increasingly relevant as medicine transitions to a population health management model in which in person contact with patients will likely decrease. This state of affairs creates the need for alternative means for clinicians to help monitor the well being of their patients remotely. In this context, the informativeness of patients' self reports is of high importance, yet surprisingly limited information on the subjects is available. The main aim of this study was to investigate the informativeness of self-reports of ADHD symptoms in adults in the clinical setting.

Methods: Subjects were clinically referred adults of both sexes ages 19-67 years (N=19). All subjects were on stable doses of long-acting stimulant medication for ADHD. The Clinical Global Impression-Improvement (CGI-I) scale for ADHD was used to determine if subjects were good responders to their stimulant medications. Only subjects considered to good responders (CGI-I score of ≤ 2) were included. ADHD symptoms were assessed using the ADHD Investigator Symptom Rating Scale (AISRS) and the ADHD Self-Report Scale (ASRS). We performed Spearman's rank correlation to examine the association between the AISRS and the ASRS. The analysis was two-tailed and performed at the 0.05 alpha level using Stata® (version 14).

Results: The average age of participants was 43.9 ± 14.4 years. Fifty-three percent of subjects were male and 95% were Caucasian. The average socioeconomic status was 1.3 ± 0.5 on the Hollingshead scale. Using Spearman's rank correlation, we found significant evidence of a strong, positive association between total scores on the clinician-rated AISRS and the patient-rated ASRS ($r(s)=0.71$, $df=17$, $p<0.001$).

Conclusions: This work adds to the available literature supporting the informativeness of self-reported assessments of ADHD symptoms. These findings have important implications for the management and monitoring of response to treatment in the clinical setting.

****S4. Early Developmental Risk Factors for ADHD Symptoms in Young Children**

Julia Schechter*[1], Naomi Davis[1], Bernard Fuemmeler[2], Susan Murphy[1], Cathrine Hoyo[3], Scott Kollins[1]

[1]Duke University Medical Center, [2]Virginia Commonwealth University, [3]North Carolina State University

Background: Early temperament and social-emotional problems tend to be stable over time and are associated with later childhood disorders. Improved understanding of the relationship between these early developmental factors and later ADHD symptoms may help identify children at-risk for developing ADHD. Early identification of ADHD can provide access to earlier interventions and may offset later negative mental health and educational outcomes.

Methods: The sample (N=94) was derived from an ongoing longitudinal study of women and children recruited prospectively from the community. Mothers completed questionnaires on child temperament and social-emotional behaviors when children were 12-24 months old and on behavior when children were 4-7 years old. The Infant Toddler Social Emotional Assessment (ITSEA) was used to measure temperament and social-emotional problems and competencies. At follow-up, mothers and teachers completed the Behavior Assessment System for Children (BASC), a commonly used broad-band behavior screener, and the Strengths and Weakness of ADHD Symptoms and Normal Behavior (SWAN), a narrow-band measure of ADHD symptoms. Linear regressions were run between ITSEA domains and relevant BASC (Hyperactivity, Attention Problems) and SWAN scales (Hyperactivity, Inattention). Child age, gender, and maternal ADHD symptoms were examined as covariates.

Results: Toddler externalizing problems predicted to later parent-reported attention problems (β=.32, t(86)=3.16, p<.001) and hyperactivity (β=.38, t(86)=3.80, p<.001) on the BASC, and these associations remained after including covariates in the model. Dysregulation in toddlers was predictive of parent reported attention problems (β=.36, t(94)=3.77, p<.001) and hyperactivity (β=.21, t(86)=2.08, p=.04), but only the association with attention problems remained significant after including covariates. Higher toddler Competence scores (e.g., attention, compliance) predicted to lower attention problems (β=-.39, t(86)=-3.95, p<.001) and hyperactivity (β=-.24, t(86)=-2.26, p=.03), though the association with hyperactivity dropped to a trend level after including covariates. Using a narrow-band measure of ADHD symptoms, toddler competencies were significantly associated with SWAN Inattention (β=.28, t(86)=2.65, p=.01) and Hyperactivity (β=.28, t(86)=2.58, p=.01), and results were consistent after including controls. Externalizing problems and dysregulation were not significantly associated with this ADHD measure. Despite significant correlations between parent and teacher reported hyperactivity on the BASC (r=.24) and SWAN (r=.40), and attention problems on the SWAN (r=.36), none of the early social-emotional or temperament measures were associated with any teacher report.

Conclusions: Social-emotional behaviors and temperament in toddlerhood are significantly associated with later attention problems and hyperactivity as measured in late preschool/early school age years. Results suggest that parent-report of these behavioral difficulties may identify children at-risk for later ADHD symptoms. Importantly, most associations were observed using a broad-band measure rather than an ADHD-specific tool, and associations were noted by parent but not teacher report. Further analyses with a larger sample will be important to clarify these trends and identify steps to support the development of young children at-risk for ADHD.

****S5. Trait Anhedonia: A Risk Factor for Undetected Attention Deficit Hyperactivity Disorder and Suicide in Adult Depressed Patients**

Tia Sternat*[1], Kathryn Fotinos[1], Alexa Fine[1], Cathy Cameron[1], Irvin Epstein Epstein[1], Martin Katzman[1]

[1]START Clinic for Mood and Anxiety Disorders

Background: Depression and suicide have become a major public health concern as rates continue to increase and have become among the leading causes of disability and death respectively. Research suggests that more than 11% of adolescents experience depression and that depressed adolescents are 6-times more likely to attempt suicide compared to non-depressed individuals. As well, adolescents with a history of attention deficit hyperactivity disorder (ADHD) are significantly more likely to develop depression by adulthood. A core symptom of depression, anhedonia3, is present in a subset of patients with ADHD and associated with poorer treatment response in patients treated with traditional antidepressants. Thus, the aim of this study was to determine predictive factors and clinical features associated with the development of treatment-resistant depression (TRD) and suicidality in patients with mood and anxiety disorders.

Methods: Data was collected from consecutive referrals to a tertiary-care mood and anxiety clinic. Only patients that provided informed consent and were new referrals were included in the analysis (n=160). Patients treated for ADHD at the time of referral with excluded from the analysis. Diagnosis was established by using the Mini International Neuropsychiatric Interview Plus 5.0.0 and a semi-structured interview by a senior psychiatrist. One-way analysis of variance and t-tests were performed to examine predictive factors related to the development of TRD and factors that may suggest an increased risk for suicidality.

Results: Results indicated that 34% of patients referred for TRD had untreated ADHD with more than 55% of these patients presenting with chronic anhedonia. Other clinical feature included SSRI failure (44%), suicide ideation (62%), and suicide attempts (16%). The number of failed psychiatric medications ($p < 0.001$), SSRI failures ($p = 0.020$), and number of past SSRI failures ($p = 0.032$) was predictive of ADHD in patients with TRD. The most predictive factor of SSRI failure within this group was the presence of chronic and present anhedonia ($p = 0.002$, $P = 0.003$, respectively) Moreover the presence of chronic anhedonia was predictive of increased reports of suicide ideation ($p = 0.05$) and attempts ($p = 0.036$).

Conclusions: These results support previous findings that ADHD is a significant risk factor for the development of TRD. This study demonstrated that the presence of chronic (trait) anhedonia or low hedonic tone may be a link between TRD and ADHD, which may predict poorer treatment outcomes in a subset of patients treated with SSRIs. Moreover, low hedonic tone may increase the risk of suicidality. These findings suggest that it is imperative to assure safety and optimal outcomes in patients presenting with depression, by ensuring accurate screening in patients that fail SSRI treatment, for concurrent ADHD, as well as low hedonic tone.

S6. Treatment Resistant Depression: A Depressive Phenotype of Attention Deficit Hyperactivity Disorder?

Tia Sternat*[1], Alexa Fine[1], Kathryn Fotinos[1], Munira Mohamed[1], Irvin Epstein[1], Cathy Cameron[1], Martin Katzman[1]

[1]START Clinic for Mood and Anxiety Disorders

Background: Blunted response to reward (anhedonia) is present in many psychiatric conditions including depression and attention deficit hyperactivity disorder (ADHD). Anhedonia is among the most treatment resistant symptoms of depression. ADHD and depression are heritable disorders that share genetic risk factors including altered reward processing. Depression severity and chronicity are positively correlated with ADHD symptomology. The aim of this study was to assess the prevalence of undetected ADHD in adults with treatment-resistant depression (TRD) and to identify clinical features that may predict the presence of ADHD and treatment outcome.
Methods: Data was collected from consecutive referrals (n=123) to a tertiary-care mood and anxiety clinic. Diagnosis was established by the Mini International Neuropsychiatric Interview Plus 5.0.0 and semi-structured interview by the treating physician. One-way analysis of variance was performed to examine factors related to presence of comorbid disorders, diagnosis of TRD, and medication history.
Results: Results indicated that undetected ADHD was present in more than 28.4% of mood and anxiety disorder referrals and 22.6% of patients with TRD. Predictive factors of undetected ADHD included number of diagnoses ($p = 0.004$), psychiatric medication history ($p = 0.001$), and number of SSRIs prescribed ($p = 0.026$). Whereas, the number of failed medications at intake ($p = 0.005$), number of diagnoses ($p = 0.006$), Social Anxiety Disorder ($p = 0.003$) and SSRI failure ($p = 0.006$) were predictive of the presence of ADHD in patients referred for TRD. The presence of chronic anhedonia predicted SSRI failure ($p = 0.002$).
Conclusions: These results support previous findings that ADHD is a significant risk factor for the development of MDD. This study demonstrated that ADHD is often undetected in adult patients referred for MDD treatment and suggests that SSRI failure is a predictor of patients being diagnosed as treatment-resistant. As well, anhedonia may serve as a prognostic indicator of the presence of ADHD and poor treatment outcomes in depressed adults. This signifies the importance of screening for ADHD in depressed patients presenting with anhedonia and the need for further studies of behavioral and neurobiological markers to guide treatment.

S7. The Relationship Between Cognitive Distortions and ADHD After Accounting for Depression, Anxiety, and Personality Pathology

Amelia Serine*[1], Brad Rosenfield[2], Robert DiTomasso[3]

[1]Center for Brief Therapy, Philadelphia College of Osteopathic Medicine, [2]ABCT, [3]Philadelphia College of Osteopathic Medicine

Background: It is theorized that some of the problems associated with adult ADHD result from cognitive distortions. Previous studies have identified a preliminary relationship between cognitive distortions and ADHD, but these studies did not measure personality pathology, which might explain part of the findings, given that personality disorders are highly comorbid with ADHD and cognitive distortions. The purpose of this study was to determine the relationship between cognitive distortions and ADHD, after accounting for personality pathology, depression, and anxiety.
Methods: A correlational research design assessed cognitive distortions, as measured by the Inventory of Cognitive Distortions; the severity of ADHD, as determined by the Brown Attention Deficit Disorder Scale; personality pathology, as determined by high Neuroticism, low Agreeableness, and low Conscientiousness on the Revised NEO Personality Inventory; anxiety, as measured by the Penn State Worry Questionnaire; and depression, as measured by the Beck

Depression Inventory-II. Data were collected on 112 adult participants from an archival database who were evaluated at an outpatient clinic specializing in ADHD. The anonymous data were exported into an SPSS file and analyzed.

Results: Six Pearson product-moment correlations were conducted. A Bonferroni correction resulted in a more stringent alpha of .008. Results indicated a significant positive relationship between ADHD and Neuroticism ($r = .295$, $p = .002$) and ADHD and depression ($r = .410$, $p = .000$). Results also indicated a significant negative relationship between ADHD and Conscientiousness ($r = -.566$, $p = .000$). The relationship between ADHD and anxiety approached significance ($r = .215$, $p = .023$). There was no relationship between ADHD and Agreeableness ($r = -.111$, $p = .245$).

A multiple linear regression was conducted using ADHD, anxiety, depression, Conscientiousness, Agreeableness, and Neuroticism scores as predictors and cognitive distortion scores as the criterion. The overall regression analysis was significant ($F = 18.673$, $p = .000$). Examining each of the predictor variables revealed that only three of the predictors made a significant contribution to the prediction: depression ($t = 3.712$, $p = .000$), anxiety ($t = 2.646$, $p = .009$), and Neuroticism ($t = 2.319$, $p = .022$).

A hierarchical multiple linear regression was conducted controlling for Neuroticism, Agreeableness, Conscientiousness, depression, and anxiety in the first level and examining ADHD in the second level. The F Change was highly significant at the .000 level. In Model 2, the F change was not significant, indicating that the severity of ADHD did not make a significant contribution to the prediction of cognitive distortions ($t = 1.295$, $p = .198$). Once again, only three variables made a significant contribution to the prediction of cognitive distortions: Neuroticism, depression, and anxiety.

Conclusions: The relationship between ADHD and cognitive distortions was not significant after accounting for the relative contribution of personality pathology, depression, and anxiety. This suggests that ADHD may be a disorder of cognitive deficit (in executive functioning) rather than a disorder of cognitive distortion. As such, treatment for adults with "pure" ADHD, without comorbidities, may require treatment focusing primarily on compensating for deficits in executive functioning, as they may have fewer cognitive distortions than adults with ADHD with comorbidities.

S8. Persistence of DSM-5 ADHD Symptoms From Childhood to Adulthood Using Clinic Referred and PCP Office Based Samples

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Background: Data from Kessler et al. (2005), a community based study, suggested that there was no age-related remission in symptoms of ADHD from childhood to adulthood and that persistence was not significantly related to age, gender, or race-ethnicity. We now present data extending the findings of Kessler et al. (2005) to a DSM-5 diagnosis of ADHD via an examination of persistence

of ADHD symptoms via retrospective recall in a large referred sample of adults with and without ADHD.

Methods: Two patient samples were pooled together from a larger study to recruit patients with and without ADHD to update and validate the ASRS v1.1 Screener for DSM-5; a referred sample of adults who were recruited as part of the NYU Adult ADHD Program and patients screened for ADHD at a primary care physician (PCP) practice in the New York area. The ACDS v1.2 was used to evaluate for ADHD and the childhood and adult/current sections of the scale were used to provide retrospective scores to measure symptoms of childhood ADHD and recent symptoms of adult ADHD, the SCID/MINI to evaluate for past and current psychiatric comorbidities, and medical history, psychiatric history, and demographics were collected.

Results: Final analysis included a total of 299 respondents across the two samples, 170 of which tested positive for adult ADHD. There was a significant correlation between child ADHD and adult ADHD ACDS scores for the total 18 DSM symptoms, as well as the 9 inattentive (IA) and 9 hyperactive-impulsive (HI) symptoms, (Spearman's rho's = .90, .88, .85, $p < .001$, respectively). Correlations remained significant when controlling for gender, race-ethnicity, childhood or adult ADHD diagnosis, current GAD, and lifetime MDD. There was also a significant correlation between meeting full criteria in childhood and meeting full criteria in adulthood for ADHD, Spearman's rho = .79, $p < .001$. This finding also remained significant when controlling for the same variables described above. The group with adult ADHD tended to have high retention of each DSM-5 symptom, with a range of 67-87% persistence for IA symptoms, and 70-96% persistence for HI symptoms. A Poisson regression analysis found that neither age nor gender were influential factors in the persistence of ADHD symptoms for total 18 item scores, IA scores, and HI scores. This held true even when stratifying the sample based on gender and only examining the adult ADHD sample.

Conclusions: 1) Using aDSM-5 referred clinic and PCP office based samples, these findings validate the results in Kessler et al. (2005) regarding the persistence of ADHD symptoms from childhood to adulthood from a community sample and extend these findings to a referred sample and a sample from a PCP practice. 2) ADHD symptomology persistence is high and significantly correlated with childhood ADHD symptom severity, but is not dependent on a variety of factors such as age, gender, or race-ethnicity, or common psychiatric co-morbid conditions.

S9. Executive Function Deficits in Pediatric Obsessive-Compulsive Disorder and Attention-Deficit Hyperactivity Disorder: A Candidate Endophenotype for OCD?

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Background: Clinical observation supports that children with obsessive-compulsive disorder (OCD) commonly have comorbid attention-deficit hyperactivity disorder (ADHD), expressed as ADHD inattentive subtype or ADHD combined subtype. Executive function (EF) deficits, construed as deficits in higher-order cognition including initiating, shifting, planning and organizing skills, have been associated to both OCD and ADHD. Endophenotypes for disorders are traits causally linked to the disorder which are uniformly abnormal in individuals with the disorder, intermediate in relatives, while normal in controls. The literature supports EF deficits (inhibitory control) as a candidate endophenotype for ADHD. This study explores whether EF

deficits may also constitute a candidate endophenotype for OCD, taking into account the presence of ADHD and the various facets of EF deficits.
Methods: Twenty-eight pediatric OCD probands and 104 relatives were administered a self-report normed instrument to assess EF deficits, the Behavior Rating Inventory of Executive Function (BRIEF). The BRIEF yields t-scores which consider a Behavioral Regulation Index (BRI) (inhibition, shifting, and emotional regulation) and a Metacognition Index (MI) (initiation, working memory, planning, organization, and monitoring). MRI, BRI and subscale t-scores were compared for OCD probands and OCD relatives (some of whom also have OCD or ADHD or both), taking into account the presence of ADHD in probands.
Results: Children with OCD had significant EF deficits as seen in BRI (t-score= 60.36) and MI (t-score = 59.93) scores. Probands had higher EF deficits in BRI (t-scores = 60.36) and MI (t-scores = 59.93) compared to relatives (BRI t-score = 53.63, MI t-score = 53.80; $t = -2.82$, $p = 0.006$). The pediatric probands with OCD and ADHD (OCD+ADHD) had significantly higher BRI (t-score = 66.57) and MI (t-score = 68.43) scores than child probands with OCD and no ADHD (OCD-ADHD) (BRI t-score = 54.14, MI t-score = 51.43, $p < 0.001$). However, when subscales were examined, only the shifting subscale was elevated even in OCD-ADHD probands (t-score = 58.64), suggesting that shifting deficits are intrinsic to OCD. When examining the relatives of OCD-ADHD probands, the shifting subscale of the BRIEF had an intermediate value in relatives of OCD-ADHD probands (t-score = 54.11).
Conclusions: The results suggest that most EF deficits in OCD are caused by the presence of comorbid ADHD and are not intrinsic to OCD. The presence of shifting deficits in children with OCD-ADHD and their relatives, however, suggests that shifting, in particular, may be an endophenotype candidate for OCD. These findings are consistent with clinical observations of cognitive inflexibility in OCD and expand upon the theoretical understanding of the disorder. Future research should further differentiate the components of ADHD in OCD to advance biological studies and formulate specific treatments.

S10. Self Perceptions of Individuals With ADHD and Learning Disabilities and Their Post-Secondary Pathways

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Background: Attributional style – the way individuals explain the causes of their successes and failures – plays an important role in academic motivation. Positive attributional style, which is generally characterized as attributing negative events to external, specific, and unstable causes, has been related to greater self-efficacy, resilience, and academic achievement. However, students with disabilities that impact their school performance are at risk for developing a negative attributional style, as they are likely to attribute their failures to limitations in their own abilities. The present study explored the impact of attributional style and self-perceptions of college students with ADHD and learning disabilities on a number of key outcomes including academic and non-academic interests, career choice, academic self-efficacy, and resilience. It was hypothesized that positive attributional style would predict greater academic self-efficacy, which in turn would predict more academic career choices.
Methods: We recruited 100 students through the disability services office at three different post-secondary institutions in New York to participate in an online survey. Participants were between

the ages of 18 and 42 (M = 20.2, SD = 2.7), approximately half were female (52%), and the majority were white (93%). Participants had a variety of diagnoses, the most common being ADHD (57%) and Dyslexia (27%). We measured attributional style, self-perception, occupational interests, resilience, and academic self-efficacy.
Results: While analyses did not support the hypothesized mediation relationship between attributional style, academic self-efficacy, and career path, results did reveal other interesting relationships between study variables. As expected, greater perceived responsibility of the disability for negative events predicted lower academic self-efficacy ($B = -.19$, $p < .05$), greater perceived globality of the disability predicted lower levels of resilience ($B = -.12$, $p < .05$), and greater perceived stability of the disability predicted less interest in both academic ($B = -.07$, $p < .05$) and non-academic areas ($B = -.07$, $p < .05$). Surprisingly, greater global and stable attributions for negative events predicted more academic career choices ($B = .93$, $p < .01$).
Conclusions: These findings suggest that individuals with ADHD and learning disabilities on a more academic career path might have more negative attributional styles. This is likely due to the salience of and challenges brought about by their disabilities in their post-secondary studies in comparison to individuals on a less academic career path. Additionally, findings suggest that the cultivation of non-academic interests could be related to more positive self-perceptions in college students with ADHD and learning disabilities. Efforts should be made to ensure that the extra time students with disabilities may need to spend on schoolwork does not interfere with their ability to participate in extracurricular activities. College counselors should be aware that despite their relative success, students with ADHD and learning disabilities attending post-secondary institutions may struggle with negative self-perceptions.

S11. Inattention and Hyperactivity-Impulsivity: Their Detrimental Effect on Romantic Relationship Maintenance

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Background: Individuals with ADHD experience social problems, including problems with romantic relationships. ADHD is associated with lower rates of marriage and an increased risk for divorce. Due to the highly distressing nature of romantic relationship problems, these experiences are an important line of investigation. The current study aims to (1) understand how ADHD symptoms correlate with romantic relationship maintenance behaviors such as, willingness to accommodate and interest in alternative relationships when a threat to the relationship is experienced, and (2) test relationship maintenance as a mediator of the relationship between ADHD symptoms and romantic relationship difficulties.
Methods: This study involved two phases of data-collection, which were identical except for the population. Phase 1 (n = 172) was a non-clinical sample of romantically-involved young adults used to test the theoretical pathways in a control sample. Phase 2 (n = 39) included a clinical sample of romantically-involved young adults with ADHD. Participants in both phases reported on their levels of inattention and hyperactivity-impulsivity symptoms, their relationship maintenance activities, and their relationship quality.
Results: ADHD symptoms were associated with greater relationship difficulties in both the clinical and non-clinical samples. In both samples, inattentive symptoms were associated with

greater interest in relational alternatives and less constructive responses to partner's bad behaviors, whereas hyperactive-impulsive symptoms were associated with negative responses to bad behavior in both samples.
Conclusions: These results may help to target content for cognitive behavioral therapy (CBT) modules designed to improve romantic relationships in young adults with ADHD.

S12. Actigraphically-Measured Sleep Disturbances and Impaired Executive Functioning in a Community Sample of Young Children

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Background: Sleep disturbances are common in children with ADHD and contribute to increased symptom severity and poorer executive functioning, suggesting a potential role of poor sleep as a risk factor for ADHD severity and related cognitive deficits. However, little is known about how sleep in early development, prior to typical age of diagnosis, may contribute to poorer clinical and cognitive outcomes. Recent community studies sampling preschool and early elementary children have revealed associations between parent-reported sleep disruptions, ADHD symptoms, and impaired executive functioning. As parent-report can be limited (e.g., cognitive biases, poor recall), the current study aimed to extend prior work by incorporating an objective sleep measure (i.e., actigraphy).
Methods: Twenty-four young children (mean age = 5) were recruited from an ongoing community study investigating relationships between maternal and child health outcomes (Newborn Epigenetics Study). Children participated in seven nights of actigraphy, which was used to derive sleep variables including Total Sleep Time (TST; duration of sleep), Sleep Efficiency (SE; percentage of time in bed spent asleep), and Wake Time After Sleep Onset (WASO; nocturnal awakenings). Concurrently, their mothers completed a daily rest/activity diary to support accuracy of actigraphy data. Parent-report measures of Inattention/Hyperactivity (Behavior Assessment System for Children-2nd Edition) and Executive Functioning (i.e., inhibition, emotional control, shifting focus, working memory, and planning/organization; Behavior Rating Inventory of Executive Function) were obtained.
Results: Partial Pearson correlations controlling for age and gender revealed that reduced TST was associated with greater parent-reported difficulties with emotional control ($p < .01$) and inhibition ($p < .05$), and reduced SE and greater WASO were correlated with increased difficulties with shifting focus ($p < .05$). Actigraphically-measured sleep disturbances were not associated with either inattentive or hyperactivity problems despite strong, positive relationships among inattentive and hyperactivity problems with parent-reported executive functioning in this sample. Actigraphically-measured sleep disturbances were not associated with working memory or planning/organization.
Conclusions: Results suggest that objectively-measured sleep disturbances are associated with poorer executive functioning, but not ADHD symptoms, in a community sample of young children. In addition, specific sleep deficits were differentially correlated with domains of executive function, suggesting that distinct aspects of sleep disturbance may convey risk for different cognitive problems in children. Lack of association between sleep and ADHD symptoms in this study may reflect limitations of the study (small sample size, parent-report of ADHD

symptoms); or perhaps, sleep's specific interference with cognition during early development may confer risk for worsened clinical outcomes in later childhood. Future longitudinal studies using large samples are necessary to further disentangle complex relationships between sleep, ADHD, and executive functioning in childhood and inform prevention and intervention efforts.

S13. Collateral Reporters Use Relationship Strength and Patient Age to Gauge Mental Health Risks

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Background: This study was designed to evaluate the use of collateral feedback (including significant other, parent, friend or other) when assessing adult patients for the likelihood of engaging in high-risk behaviors including: eating too little on purpose; binge eating and/or purge after eating; self-isolating or withdrawing socially; gambling too much; drinking too much alcohol; misusing legal drugs; using illegal drugs; physically hurting oneself on purpose (not a suicide attempt); physically hurting someone else on purpose; and committing suicide.
The primary objective was to measure the correlation between collateral and self-reported assessments of risk in those domains. The study also assessed how relationship quality affected the level of agreement between collateral and self-assessments of risk in several domains.

As AD/HD is highly comorbid with other mental health disorders including substance use disorders and disorders of impulse dyscontrol, this study is highly relevant to clinicians who evaluate and treat adults with AD/HD.

Methods: Participants were initially recruited from the patient population at the Rochester Center for Behavioral Medicine (RCBM) in Rochester Hills, Michigan. All adults presenting for diagnostic screening at RCBM were asked if they would be willing to participate in a research study. Each patient who agreed was also asked to nominate a "collateral reporter" who they felt knew them well enough to report about their mental health. RCBM staff contacted those collateral reporters by postal mail. Each participant was asked to complete two brief surveys; one survey asked the likelihood that they would do each of the listed high-risk behaviors. The second survey asked them to assess the quality and closeness of their relationship with the collateral reporter. The collateral reporter completed the same two surveys about their loved one. Follow-up surveys (identical to the initial surveys) were administered six weeks into treatment (Time 2).
Results: Moderately strong positive correlations were observed for risk and for relationship at Time 1 and Time 2. Patients in stronger relationships were rated slightly less at risk overall. After controlling for this effect, female patients were judged at increased risk, but only because of the effect of their age.
When examining only the data from the collateral reporters, it was shown that perceived risk was negatively predicted by relationship strength. This effect was fully mediated by patient age. Patient age was again negatively predictive of perceived risk.

Conclusions: Taken together, the results of the present study demonstrated that collaterals and patients generally agreed about risk for a variety of high-risk behaviors. Additionally, the degree of perceived risk was predicted by a patient's age, gender, and relationship strength.

These results contribute to an existing literature suggesting that the best risk assessments involve a variety of collateral observers from different domains, and assess for a number of variables. This is particularly important in the AD/HD community so that high-risk behaviors associated with this disorder and its comorbidities can be teased out from the onset of treatment.

It is advocated here that collateral information can be used to supplement existing assessment by clinicians in an effort to work collaboratively to reduce risky behaviors that could otherwise adversely impact schools, communities, and patients' lives.

S14. Is Paternal Smoking at Conception a Risk for ADHD? a Controlled Study in Youth With and Without ADHD

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Background: Emerging preclinical findings suggest that paternal smoking during at conception may be a risk for ADHD in the offspring. The aim of this study was to investigate whether similar effect can be observed in humans.

Methods: Subjects were female probands aged 6-18 years with (N=140) and without (N=122) ADHD. Information about paternal smoking at conception was based on direct structured diagnostic interviews with the fathers that assessed smoking onset and smoking offset. Data were analyzed using Pearson's chi-square tests and multiple logistic regression.

Results: Out of the 262 total probands, 23 did not have the information needed to determine paternal smoking at conception and 13 had fathers with uncertain smoking status. Thus our final sample consisted of 121 ADHD probands, 105 control probands, and their 226 fathers. The ADHD and control probands were of similar age and socioeconomic status (Table 1). ADHD probands had a significantly higher rate of paternal smoking at conception than controls (35% vs. 23%, $\chi 2=3.82$, $p=0.05$). Although the odds ratio of paternal smoking at conception were 1.5 even after adjusting for paternal ADHD, the association between paternal smoking at conception and proband ADHD status lost significance after controlling for paternal ADHD (OR=1.50, $\chi 2=1.58$, $p=0.21$), most likely due to limited statistical power.

Conclusions: Paternal smoking at conception was significantly higher in fathers of ADHD probands than in fathers of controls. Despite limited statistical power, findings suggest that paternal smoking at conception may be a risk factor for ADHD in the offspring. More work is needed to further evaluate whether paternal smoking at conception increases the risk for ADHD in offspring of both sexes.

S15. Atomoxetine-Related Change in Sluggish Cognitive Tempo is Largely Independent of Change in Attention-Deficit/Hyperactivity Disorder Inattentive Symptoms

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Background: Although Sluggish Cognitive Tempo (SCT) and Inattention (severity of Inattention symptoms from DSM-V ADHD; IN) appear to be separate dimensions when evaluated cross-sectionally, little is known about what implications this may have for treatment. We conducted a post-hoc analysis of symptom change in a 16-week placebo-controlled, double-blind, randomized trial of atomoxetine in children ages 10-16 years with ADHD+Dyslexia, Dyslexia-only, or ADHD-only (this latter group was not exposed to placebo).
Methods: Least squares mean changes from baseline to endpoint for atomoxetine versus placebo on the Kiddie-Sluggish Cognitive Tempo Interview (K- SCT) (Parent, Teacher, and Youth) were analyzed using analysis of covariance and multiple regression (partial R2) analyses to test contributions of ADHD and dyslexia to improvements in K-SCT scores.
Results: Results were examined for the three informants within the three diagnostic groups (nine outcomes). When change in ADHD symptom severity was controlled, all of the seven SCT outcomes remained significant at $p = 0.05$, and only one outcome became nonsignificant at $p = 0.02$; changes in effect sizes were minimal. Regression analyses using SCT change as the criterion found a significant contribution by Inattention change only for parent report, whereas, baseline SCT severity was a significant predictor in the randomized group with the exception of teacher report in the Dyslexia-only group.
Conclusions: Given that controlling for change in ADHD symptoms had little effect on change in SCT scores, findings suggest that change in SCT is substantially independent of change in ADHD. By inference, SCT and its response to treatment are a partially distinct phenomena from ADHD response. Regression analyses did not reveal global effects of Inattention change on SCT change; instead, baseline SCT severity was the strongest predictor of placebo-controlled treatment effect on SCT. Atomoxetine effects on SCT appear to be best predicted by how much room for improvement exists for SCT, rather than by severity or improvement in Inattention.

**S16. Treating Mothers First: Acceptability and Engagement in Pharmacological Treatment and Behavioral Parent Training for Mothers With ADHD

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Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is highly familial; maternal ADHD affects mother and child health and functioning. Treating Mothers First (TMF) is a Sequential Multiple Assignment Randomized Trials (SMART) Pilot for mothers with ADHD evaluating 8 weeks of either pharmacological treatment (MED) or behavioral parent training (BPT), followed by 8 weeks of the same or opposite intervention. Little is known about the acceptability and engagement of mothers with ADHD in treatments to improve their functioning, parenting, and children's outcomes.
Methods: Mothers who had received no prior effective treatment for ADHD with children between the ages of 3 and 8 years at risk for ADHD were recruited for the 16-week study from outpatient clinics and the community. Maternal ADHD diagnosis was confirmed with clinical

interview and administration of the Adult ADHD Clinical Diagnostic Scale (ACDS) and the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) by a clinical psychologist. At treatment entry, mothers were randomized to receive an initial 8 weeks of either a lisdexamfetamine medication strategy managed by a psychiatrist (MED) versus weekly BPT sessions based on Russell Barkley's "Defiant Children" curriculum with a licensed psychologist or supervised trainee. At the end of week 8, mothers were re-randomized to continue the initial treatment versus MED+BMT for an additional 8 weeks.
Treatment engagement was measured with rates of drop-out, timeliness to and consistency of appointments, and medication adherence, as well as mother and therapist ratings at week 8 and 16 of BMT on the Treatment Adherence Inventory. Acceptability of treatment was evaluated with mother report on the Acceptability and Feasibility Questionnaire (AFQ) as well as open-ended qualitative surveys at the conclusion of the study.

Results: 35 mothers (mean age = 39) were randomized to four conditions: MED/MED (n=9), MED/BPT (n=9), BPT/MED (n=9), and BPT/BPT (n=8). Mothers were predominately Caucasian (92%), Not Hispanic/Latino (92%), and married (79%). The majority of mothers were diagnosed with ADHD, predominately inattentive presentation (54%), followed by combined presentation (29%) and hyperactive/impulsive presentation (17%).
Three participants dropped out at week 8 when assigned to the same condition for the second phase of the study, and one dropped after week 1 (MEDS). Session attendance was high across conditions. Trends indicated that mothers who received BPT after meds (MED/BPT) were more satisfied with assignment to BPT than those receiving BPT/BPT. Mothers who received MED/BPT felt more satisfied with the overall study assessment and procedures. Mothers who received BPT/BPT reported that appointments were more burdensome than mothers receiving 8 weeks of BPT.

Conclusions: Pharmacological treatment and BPT are acceptable interventions for mothers with ADHD and engagement was high. Treatment satisfaction was greater for mothers receiving combined treatment.

**S17. Medication Adherence in Pediatric and Young Adult Patients Prescribed ADHD Stimulants

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Background: Substance use by pediatrics, adolescents, and young adults is a public health issue that encompasses both illegal drug use and nonmedical use of prescription medications. Both nonadherence to and diversion of prescribed stimulant ADHD drugs (ADHDD) are common in adolescents and young adults. More than one-half (54%) of college students and up to one-quarter (23%) of middle and high school students had been approached to divert their prescribed ADHD stimulant medications.
The objective of the study is to identify potential nonadherence among pediatric, adolescent, and young adult patients prescribed attention-deficit/hyperactivity disorder (ADHD) stimulant medications and assess the differences in illicit substance and/or nonprescribed medication use in patients testing positive versus negative for the ADHD medication.

Methods: Urine samples submitted to the laboratory between 2014 and 2016 from patients 6 to 25 years old, inclusive, who were documented on the laboratory requisition to have been prescribed an amphetamine or methylphenidate medication for the treatment of ADHD were included in the analysis. The first urine sample obtained from each patient was analyzed for the presence of the prescribed ADHD medication, illicit substances (marijuana metabolite [THCA] and cocaine metabolite [benzoylecgonine]), and select nonprescribed opioid or benzodiazepine medications.
Results: Samples were analyzed from 4449 patients; 66.4% of patients were male and the mean±SD age was 14.1±5.5 years. Overall, 30.2% of patients tested negative for their prescribed ADHD medication. Patients aged 6 to 10 years had the lowest rate of negative test results (21.0%) and patients aged 18 to 21 years had the highest rate (45.5%; adjusted odds ratio [aOR], 3.2; 95% confidence interval [CI], 2.5-4.1). Illicit substances, primarily THC, were rarely detected for patients under age 14, but were detected in 11.8%, 20.8%, and 20.0% of patients 14 to 17, 18 to 21, and 22 to 25 years, respectively. Detection of nonprescribed opioid medications was rare in patients <18 years old, but were found in 7.7% and 11.4% of patients 18 to 21 and 22 to 25 years, respectively. Patients who tested negative for prescribed ADHD medication were significantly more likely than patients who tested positive to have THC detected in the urine sample (17.3% vs 7.1%; aOR, 1.9; 95% CI, 1.5-2.4).
Conclusions: Urine drug monitoring in patients prescribed stimulant ADHD medication can be of value both for evaluating adherence to ADHD therapy and identifying the inappropriate use of illicit substances and/or nonprescribed medications. The data suggest that potential nonadherence to prescribed stimulant ADHD therapy is associated with marijuana use and that detection of marijuana in children as young as 14 to 17 years is not uncommon.

**S18. Establishing Clinical Benefit of HLD200, a Novel Delayed-Release and Extended-Release Formulation of Methylphenidate, Using a Model-Based Approach

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Background: Several extended-release formulations of methylphenidate (MPH), usually characterized by a dual release process, have been developed for the treatment of attention-deficit/hyperactivity disorder (ADHD). HLD200 is the first and only evening-dosed delayed-release and extended-release formulation of MPH that utilizes a novel drug delivery system (DELEXIS®) designed to delay initial drug release by approximately 8-10 hours, targeting the onset of clinically meaningful treatment effect upon awakening and throughout the day. The purpose of this study was to develop pharmacokinetic (PK) and PK/pharmacodynamic (PD) models for HLD200 to establish its clinical response versus two currently available extended-release MPH (ie, OROS MPH and MPH CD).
Methods: A population PK model was developed by using data collected from 25 sampling tests of a phase 1 PK study in 20 healthy adults receiving HLD200 (20 mg or 100 mg), and evaluating alternative in vivo release models. A PK/PD model was also developed by using the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP) scores over 9 sampling times in a randomized phase 3 trial of children with ADHD receiving either HLD200 (n = 64) or placebo (n = 53). An indirect response model described the trajectories of SKAMP scores following placebo

administration and a maximum effect (Emax) model characterized the drug-related change from placebo. Clinical benefit of HLD200, based on changes from placebo, was compared with the published data of OROS MPH and MPH CD.
Results: The best performing PK model was a one-compartment model with a time varying absorption rate described well by a single Weibull in vivo release function. Covariate analysis identified that volume of distribution was weight-dependent and gender affected the time of MPH release from HLD200. The placebo response model properly described SKAMP score trajectories, and the population PK/PD model established an exposure-response relationship, where a drug concentration of ~15 ng/mL is necessary to induce an improvement in clinical response by ~40%. Covariate analysis indicated an effect of gender on the half maximal effective concentration (EC50). HLD200 (~65 mg) was found to provide a clinical benefit that is comparable with medium-to-high doses of OROS MPH and MPH CD, and produced a more constant and less fluctuating response throughout the day. Furthermore, HLD200 had a clinical response earlier in the day compared with OROS MPH and MPH CD, and a dose-dependent duration of clinical response that lasted into the evening hours.
Conclusions: The population PK/PD model developed for HLD200 provided a reasonable estimate of its clinical benefit. When compared with OROS MPH and MPH CD, the model revealed that HLD200 produces a clinical response that occurs earlier in the day, remains constant with less fluctuation throughout the day, and has a dose-dependent duration of effect that lasts into the evening.

**S19. Daily Average Consumption (DACON) Among Commercially-Insured Adults With Attention-Deficit Hyperactivity Disorder (ADHD) Who Received Monotherapy in the US

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Background: Long-acting (LA) and short-acting (SA) pharmacotherapies are recommended for the treatment of adults with ADHD. The labeled DACON is 1 tablet per day for LA agents and 2 tablets per day for SA agents when prescribed as monotherapy and patients are fully adherent. However, it is unknown how adults use ADHD monotherapy in real life. The current study aims to examine real-world DACON of ADHD monotherapy among commercially-insured adults with ADHD in the US.
Methods: Adults with ≥1 record of an ADHD diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 314.0 or 314.9) and receiving ≥1 ADHD medication in 2013 were identified from the Truven Marketscan claims database. Patients receiving monotherapy in the first treatment episode in 2013 were further selected into the final analysis. Specifically, a treatment episode was defined as continuous use of a treatment until treatment discontinuation, denoted as a gap of >30 days in the drug supply. The first ADHD treatment with an episode of ≥30 days in 2013 was defined as the index treatment, and the corresponding episode was the index treatment episode. Monotherapy was defined as no concomitant use of other ADHD medications with the index treatment for ≥30 days during the index treatment episode. The main outcome of the study was DACON, calculated as the ratio of the number of tablets of the index treatment dispensed and the number of days of supply during the index treatment episode. Means and standard deviations (SDs) of DACON and the proportion

of patients receiving monotherapy greater than labeled DACON were reported for patients receiving LA and SA monotherapy as the index treatment, respectively.
Results: A total of 117,409 patients (65.0%) receiving LA monotherapy and 63,301 patients (35.0%) receiving SA monotherapy as the index treatment were included. The mean age was 31.9 (SD=13.0) years for LA monotherapy users and 35.0 (SD=12.7) for SA monotherapy users. 50.7% of LA monotherapy users and 53.6% of SA monotherapy users were female. The mean DACON was 1.2 (SD=0.6), and 2.1(SD=0.9) among the LA and SA monotherapy users, respectively. 20.2% of LA monotherapy users had DACON>1, and 28.5% of SA monotherapy users had DACON>2.
Conclusions: A notable proportion of adult ADHD patients on LA and SA monotherapies had higher than labeled DACON, suggesting that they might not achieve adequate symptom control using labeled dosing regimens of a single medication. These patients might benefit from medications which provide longer control of symptoms.

**S20. The Efficacy and Safety of Amphetamine Extended-Release Oral Suspension (Amph Eros) in Children With ADHD

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Background: To determine the efficacy and safety of amphetamine extended-release oral suspension (AMPH EROS) in the treatment of attention-deficit/hyperactivity disorder (ADHD) compared to placebo in a dose-optimized, randomized, double-blind (DB) study.
Methods: Male and females aged 6-12 years diagnosed with ADHD were enrolled. Subjects began treatment with 2.5 mg or 5 mg/day of AMPH EROS and were titrated in 2.5 to 10 mg/day increments until an optimal dose (maximum 20 mg/day) was reached. The dose could be decreased for tolerability reasons. During the double-blind phase, subjects were randomized to receive treatment with either their optimized dose of AMPH EROS or placebo for 7 days. On Day 7, subjects completed a laboratory school day. Drug efficacy was assessed prior to dosing of AMPH EROS and at 1, 2, 4, 6, 8, 10, 12 and 13 hours post-dose using the SKAMP (Swanson, Kotkin, Agler, M-Flynn, and Pelham) Rating Scale. Safety was assessed measuring vital signs and adverse events (AEs).
Results: The primary efficacy endpoint, the change from pre-dose SKAMP-Combined score at 4 hours post-dose; and the key secondary endpoints, change from pre-dose SKAMP-Combined scores at 1, 2, 6, 8, 10, 12 and 13 hours post-dose were statistically significant ($p<0.0001$) versus placebo. Adverse events (>5%) reported during dose optimization were decreased appetite, insomnia, affect lability, upper abdominal pain, mood swings and headache.
Conclusions: AMPH EROS was effective in reducing symptoms of ADHD from 1 to 13 hours after dosing. Adverse events reported were consistent with those of other amphetamine products.

S21. Pooled Safety and Tolerability Data of Metadoxine Extended Release (MDX) From Three 6 Week Placebo Controlled Clinical Studies Pooled Safety and Tolerability Data of Metadoxine Extended Release (MDX) From Three 6 Week Placebo Controlled Clinical Studies

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Background: Metadoxine Extended Release (MDX) is a once-daily, dual-release oral formulation of metadoxine, demonstrated to be a modulator of GABAergic transmission with a monoamine-independent mechanism of action. Previous phase 2 and 3 placebo-controlled studies have demonstrated a favorable clinical safety profile of MDX in adults with Attention Deficit Hyperactivity Disorder (ADHD) and in adolescents and adults with Fragile X Syndrome (FXS). The current retrospective analysis sought to characterize the safety profile of MDX based on pooled data from the three 6-week placebo controlled clinical studies with MDX completed to date.

Methods: Data from three double-blind, placebo- controlled studies were pooled. The first study was a 6 week phase 2 study including 120 adults with ADHD (Study AL008), the second study was a 6 week phase 3 study including 300 adults with ADHD (Study AL012) and the third study was a 6 week phase 2 study including 62 adolescents and adults with Fragile X Syndrome (FXS) (Study AL014). Data presented herein were analyzed for rate, severity and nature of adverse events in subjects on MDX treatment compared to placebo, rate of study discontinuations, and rate of significant changes in the following safety parameters: Vital Signs, Weight, Laboratory assessments (chemistry, hematology, urinalysis), ECGs, Assessment of Suicidal Behavior, Neurologic Exam and Physical Exam.

Results: The safety population in the pooled data of the three studies included 478 subjects, 416 in the two ADHD studies and 62 in the FXS study. Of these, 419 (88%) completed the studies. Similar rates were found for MDX or placebo subjects, 89% and 87% respectively.

The total number of subjects withdrawing early from the studies was 59 (12%). The number of subjects who withdrew due to non-compliance with study medication or adverse events was relatively low (23, 4.8%). More subjects in the placebo group withdrew because of non-compliance (MDX 2, Placebo 6) and more subjects in the MDX group withdrew because of adverse events (MDX 9, Placebo 6).

The number of subjects reporting AEs was similar between the MDX and placebo treatment groups in all three studies. Over all 3 studies, the most common AEs (>5% in the MDX group) were headache (18% in both MDX and placebo), fatigue (12% in MDX, 13% in placebo) and nausea (10% in MDX, 4% in placebo).

In all three studies, no drug-related serious AEs were reported and no significant changes were observed in vital signs, weight, labs (chemistry, hematology, urinalysis), neurologic exam, physical exam, ECGs, and Assessment of Suicidal Behavior.

Conclusions: Pooled data from two 6 week placebo-controlled studies of adults with ADHD and one 6 week placebo-controlled study of adolescents and adults with Fragile X Syndrome were analyzed to characterize the clinical safety and tolerability profile of MDX in these three completed studies. The findings did not show any tolerability concerns nor demonstrate any significant safety signals in a 6 week treatment duration. The data to date suggest that a sizeable population of subjects with ADHD or FXS treated with MDX for up to 6 weeks demonstrates a favorable safety and tolerability profile with this investigational drug.

S22. MEASURE: A Phase 3 Placebo-Controlled Study of Metadoxine Extended Release in Adults With Attention Deficit Hyperactivity Disorder

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Background: Prior phase 2 placebo-controlled studies with Metadoxine Extended Release (MDX) have demonstrated efficacy signals in adults with Attention Deficit Hyperactivity Disorder (ADHD). A previous phase 3 study did not result in a statistically significant benefit of MDX over placebo, and demonstrated a large placebo response and large overall response variability. A second phase 3 study, MEASURE, was designed with the goal of reducing placebo response and response variability. This analysis will examine interim blinded data from MEASURE.

Methods: MEASURE is a phase 3, 10-week, multicenter, randomized double-blind, parallel-group, fixed-dose study of MDX 1400 mg compared with placebo in adults with ADHD.
Eligible subjects have ADHD based upon DSM5 criteria with a CGI-S of 4 or greater.

Subjects enter a Screening phase and have an assessment with the Conners Adult ADHD Rating Scale: O-SV (with the investigator as observer) with adult ADHD prompts (CAARS-Inv). Subjects taking ADHD medications at Screening have a Washout period. Quality verification measures are incorporated in the study to ensure data quality and validity.

After Screening and Washout, subjects are randomized to MDX 1400 or placebo and treated for 10 weeks. During this period, all subjects are exposed to a variable period of placebo treatment. The start of the placebo period and the duration of the placebo period are blinded to both subjects and investigators. There is a two-week Follow-up period after the last dose of study treatment.

This blinded analysis examined baseline demographics (age, gender, race, ethnicity), safety data (adverse events, vital signs, neurological exam, physical exam, ECG, urinalysis, safety labs) and overall standard deviation of the change from baseline to last observation carried forward (LOCF) of the CAARS-Inv.

Results: As of October 12, 2016, 324 subjects were included in the safety population and 282 subjects were in the full analysis set (subjects with at least one post-randomization efficacy assessment). 39 (12.0%) subjects discontinued from the study, including 3 (0.9%) subjects who discontinued due to an adverse event. Demographic data showed that 152 (46.9%) subjects were male, 273 subjects (84.3%) were white and 300 subjects (92.6%) were non-hispanic/latino. The mean age of the subjects was 36.4 years (standard deviation (SD) 9.84), and the mean baseline CAARS score was 35.9 (SD 7.83).
The most common adverse events (≥ 3%) in the blinded review were headache (5%), nasopharyngitis (3%), fatigue (3%), nausea (3%), and upper respiratory tract infections (3%). There were 2 serious adverse events, cholecystitis and asthma exacerbation, both of which were considered to be unrelated to investigational product. Analysis of blinded safety data did not reveal any significant safety concerns, and IDMC periodic review of safety data in closed sessions recommended trial continuation.

The overall standard deviation of the change in CAARS-Inv from baseline to LOCF was 9.64 (n=282). This is in contrast to the overall standard deviation from the previous phase 3 study of MDX (12.04; n=297).

Conclusions: Interim blinded results from a phase 3 placebo-controlled study of MDX in adults with ADHD did not identify any significant safety concerns. The standard deviation was lower than that seen in the previously reported phase 3 study of MDX, suggesting that the design elements may have contributed to a reduced treatment response variability.

S23. Dasotraline in Children With Attention Deficit Hyperactivity Disorder: Results: of a Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study

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Background: Dasotraline is a novel and potent dopamine and norepinephrine reuptake inhibitor (DNRI) with slow absorption and a long half-life, resulting in stable plasma concentrations over 24 hours with once-daily dosing (Hopkins et al, Clin Drug Investig 2016). Safety and efficacy of dasotraline have been demonstrated in a phase 2 study in adults with ADHD (NCT01692782: Koblan et al, Neuropsychopharmacology 2015). This study evaluated efficacy, safety, and tolerability of dasotraline in children with ADHD (NCT02428088).

Methods: Children aged 6–12 years old meeting DSM-5 criteria for ADHD were randomized 1:1:1 to 6 wks of double-blind, once-daily, dasotraline (2 or 4 mg/d) or placebo. The primary efficacy endpoint was the change from baseline (CFB) in the ADHD Rating Scale Version IV – Home Version (ADHD RS-IV HV) total score at Wk 6, analyzed using a mixed model for repeated measures (MMRM) in the intent-to-treat population. Secondary endpoints included ADHD-RS-IV HV at Wks 1–5 (and subscales at Wks 1–6), Clinical Global Impression-Severity scale (CGI-S), safety and tolerability, vital signs, and weight.

Results: Of the 342 patients randomized, mean age was 9.1 [±1.9] years and 66.7% were male. Overall, 79% of patients completed the study; 87% of which continued into a 26-wk open-label safety study (NCT02457819). Adverse events (AEs) were the most common reason for discontinuation (2 mg/d: 6.3%; 4 mg/d: 13%; placebo: 1.7%). In the intent-to-treat population (n=336), ADHD-RS-IV HV total score improved significantly from baseline to Wk 6 with dasotraline 4 mg/d vs placebo (least squares [LS] mean CFB: −17.53 [95% CI: −20.12, −14.95] vs −11.36 [−13.89, −8.83], respectively; effect size (ES): 0.48, $p<0.001$). With dasotraline 4 mg/d, a statistically significant difference from placebo treatment was maintained each wk through Wk 6. Additionally, both the inattentive and hyperactivity/impulsivity subscale scores were significantly improved with 4mg/d vs placebo at Wk 6 ($p=0.001$ and $p=0.003$, respectively). The 2 mg/d arm did not demonstrate a statistically significant difference from placebo (LS mean CFB: −11.80 [−14.37, −9.22]; ES: 0.03, $p=0.812$). Improvements in CGI-S scores were statistically significant with 4 mg/d vs placebo at all time points (Wk 6 LS mean CFB: −1.39 [−1.63, −1.15] vs −1.04 [−1.28, −0.80], respectively; ES: 0.29, $p=0.040$). The 2 mg/d dose did not separate at Wk 6 (LS mean CFB: −0.94 [−1.18, −0.70]; ES: 0.08, $p=0.575$). Treatment-emergent AEs (TEAEs) were generally mild or moderate in severity; the most frequent (≥5% and greater than placebo) were (2

mg/d; 4 mg/d; placebo): combined insomnia (15.3%; 21.7%; 4.3%), decreased appetite (12.6%; 21.7%; 5.2%), weight loss (5.4%; 8.7%; 0), irritability (3.6%; 7%; 6%), nasopharyngitis (0.9%; 5.2%; 0.9%), and nausea (0; 5.2%; 2.6%). Overall, 0.9%, 2.6%, and 1.7% of patients experienced severe TEAEs. There were no serious TEAEs. The TEAE most frequently associated with discontinuation was insomnia (1.8%; 3.5%; 0). Mean supine heart rate CFB at Wk 6 was (2 mg/d; 4 mg/d; placebo) 2.3, 5.9, and 1.1 bpm. Mean weight CFB at Wk 6 was (2 mg/d; 4 mg/d; placebo): −0.42, −1.24, and +0.99 kg.
Conclusions: Dasotraline 4 mg/d, but not 2 mg/d, significantly improved ADHD symptoms in children compared to placebo, as measured by ADHD-RS-IV HV total score and inattentiveness and hyperactivity/impulsivity subscale scores. Dasotraline was generally well-tolerated with an AE profile consistent with its DNRI mechanism of action. Studies evaluating longer term use are in progress.

S24. Pharmacokinetics of a Novel Amphetamine Extended-Release Oral Suspension in Children With Attention-Deficit/Hyperactivity Disorder

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Background: Extended-release amphetamine (AMP) is a first-line treatment for attention-deficit/hyperactivity disorder (ADHD). An extended-release AMP oral suspension formulation has been developed to facilitate medication ingestion and to tailor dose titration to meet individual patient needs. The objective of this study was to determine the pharmacokinetic (PK) profile of the extended-release AMP liquid suspension in children with ADHD, under fasted conditions.
Methods: This was a single-dose, open-label, single-period, PK study conducted in 29 pediatric participants with ADHD (aged 6–12 years). Participants were stratified into 3 age groups (6–7 years, 8–9 years, and 10–12 years) and were dosed with 15 mL extended-release AMP liquid suspension (equivalent to 30 mg mixed amphetamine salts [MAS]) after an overnight fast. Blood samples were collected at prespecified time points and analyzed for d-and l-amphetamine concentrations. The following PK parameters were determined: maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), elimination rate constant (λz), elimination half-life (T1/2), area under the curve from time 0 to last quantifiable concentration (AUClast) and to infinity (AUCinf), oral clearance (CL/F), and volume of distribution in the terminal phase (Vz/F). Weight-normalized CL/F, Vz/F, and AUClast; and the 95% confidence intervals (CIs) about the geometric means of the weight-normalized parameters in each age group were calculated to determine if the 95% CIs were within the 60%–140% target range. Safety was also assessed.
Results: Of the 29 participants enrolled (mean [standard deviation (SD)] age 8.8 [1.75] years, 75.9% male, 65.5% African American), all completed the study. In general, as age increased, mean maximum and total exposure to amphetamine decreased, and weight-normalized CL/F slightly increased. The increase in CL/F resulted in a decrease in T1/2 with age. The 95% CIs for the geometric means of CL/F/kg and Vz/F/kg for d- and l-amphetamine were within 60%–140% for Group 2 (8–9 years) and Group 3 (10–12 years); pharmacokinetic variability was somewhat higher in Group 1 (6–7 years). However, the 95% CIs for the geometric mean of weight-normalized AUClast for both amphetamine enantiomers were within 60%–140% for all age groups. A total of 12 participants (41.4%) experienced 14 treatment-emergent adverse events (TEAEs) including

sinus tachycardia (10 subjects [34.5%]), vomiting (3 subjects [10.3%]), and nausea (1 subject [3.4%]). All TEAEs were mild with 12 considered treatment related.
Conclusions: Exposure (Cmax, AUC) to amphetamine decreased with age; the age-related decrease in exposure may be attributed to the 30-mg/15-mL fixed dose in this study across a wide range of weights (20–57 kg) in the 6–12-year-old participants and the consequent lower dose per kg in older participants, as well as the slight increase in clearance with age. Extended-release AMP oral suspension was well tolerated; there were no serious or severe adverse events.

S25. Proof-Of-Concept Study Results: of an Interactive Digital Treatment for Pediatric ADHD and Follow-Up Registration Study Design

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Background: Pharmacological interventions are well established in the treatment of ADHD in pediatric patients but are not always readily accepted by parents, may not provide adequate response and are associated with unwanted side effects. An exploratory proof of concept study was conducted to assess the safety, feasibility, and beneficial effects of a novel, interactive and adaptive digital cognitive intervention in pediatric Attention Deficit Hyperactivity Disorder (ADHD) participants and age-matched controls. Positive results of this study would be further confirmed with a Phase 3 Registration trial.
Methods: Participants included 40 children with ADHD and 40 controls (Mean Age = 10.3 years), recruited from 3 U.S. sites. Following psychiatric screening, ADHD ratings, and baseline neuropsychological measures, participants completed 28-days of at-home treatment, which consisted of 5 weekly 30-minute sessions using proprietary software on a digital tablet. Neuropsychological assessments were repeated at end-of-study along with treatment satisfaction measures. Measures of cognitive function (TOVA, CANTAB) and behaviors (Parent-BRIEF) were collected at Screening and Post-Intervention. Tolerability, compliance and acceptability were also assessed.
Results: PILOT STUDY: Safety and Feasibility: No treatment related adverse events were reported. Across all participants, 84% of all prescribed in-home sessions were completed, and ratings showed a strong intervention appeal. Efficacy Outcomes: The Attention Performance Index composite score from the TOVA improved significantly from pre- to post- intervention ($p = 0.033$, Cohen's $d = 0.35$) in the ADHD group. At study endpoint, there was no change in the neuro-typical group ($p = 0.30$, Cohen's $d = 0.16$). A post-hoc sub-population analysis of a group of ADHD participants with greater cognitive and symptom severity at Baseline (TOVA API <= -1.8 & ADHD-RS >=30) showed a larger effect of the intervention ($p = 0.003$, Cohen's $d = 0.71$). Multiple sub-components of the TOVA, including reaction time variability, also showed significant improvement. The ADHD group showed significant improvement on 8 of 12 variables within the CANTAB Spatial Working Memory (SWM) test, while the neuro-typical group improved on 5 of 12 variables within the SWM. For the Parent-BRIEF, the ADHD group showed improvements for working memory, however this measure did not meet the alpha criterion for multiple comparisons. No change was found for the Parent-BRIEF in the neuro-typical population.

REGISTRATION STUDY DESIGN: These pilot study results prompted the design and initiation of a randomized, controlled, parallel-group, intervention pivotal study to assess the safety and efficacy of an at-home 28-day treatment with this multitasking digital intervention versus a non-multitasking digital intervention. Outcomes for this registration trial include attentional functioning, working memory and objective inhibition as well as changes in ADHD symptoms assessed by clinician- and parent-rated ADHD scales.

Conclusions: The positive results of the Proof-of Concept study provided initial support for this novel interactive digital intervention as a potential treatment for attention and working memory symptoms in pediatric ADHD populations. The ongoing registration trial is expected to be completed in 2017.

S26. Pharmacokinetics and Relative Bioavailability of an Extended-Release Chewable Tablet of Methylphenidate When Chewed Versus Swallowed Whole: A Pilot Study in Healthy Subjects

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Background: This study assessed the pharmacokinetics (PK) and relative bioavailability of a methylphenidate hydrochloride extended-release chewable tablet formulation (MPH ERCT) when chewed versus swallowed whole in healthy adult subjects.

Methods: This randomized, open-label crossover trial enrolled healthy subjects aged 22 to 62 years. Subjects were randomly assigned to a single 40 mg dose each of a MPH ERCT prototype formulation chewed or swallowed whole, or MPH ER oral suspension, which was included as a reference formulation. Treatments were given under fasting conditions in 3 dosing periods, with a 7-day washout period between treatments. Blood samples were taken predose and at selected time points up to 24 hours after dosing. PK parameters were analyzed using a noncompartmental approach. Safety assessments included the incidence of adverse events (AEs).

Results: A total of 12 subjects were enrolled; 9 subjects completed the study and were included in the PK analysis. Mean Cmax values for MPH ERCT chewed, MPH ERCT swallowed whole, and MPH ER oral suspension were 11.98 ng/mL, 11.50 ng/mL, and 11.9 ng/mL, respectively; mean t1/2 values were 4.94 h, 5.31 h, and 5.95 h, respectively. Geometric mean AUC0-t and AUC0-inf values for MPH ERCT chewed, MPH ERCT swallowed whole, and MPH ER oral suspension showed similar exposure (AUC0-t : 94.78, 95.15, and 95.55 ng·h/mL, respectively; AUC0-inf: 98.62, 99.98, and 100.83 ng·h/mL, respectively). Geometric mean ratios of PK parameters for MPH ERCT chewed versus MPH ERCT swallowed whole were within 90% confidence limits (80%–125%) for bioequivalence: Cmax (104.20%, 95% CI: 93.95–115.56); AUC0-t (99.62%, 95% CI: 89.38–111.03); and AUC0-inf (98.64%, 95% CI: 89.01–109.32). The PK profiles of MPH ERCT chewed and MPH ERCT swallowed whole were similar. All AEs were mild in intensity across treatment groups.

Conclusions: The bioavailability of a single 40 mg dose of MPH ERCT chewed was comparable with that of MPH ERCT swallowed whole and MPH ER oral suspension. All treatments were well tolerated with no new safety signals identified.

S27. Dose Proportionality and Effect of Food on the Pharmacokinetics of HLD200, a Delayed-Release and Extended-Release Methylphenidate Formulation, in Healthy Adults

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Background: HLD200 is the first and only oral evening-dosed formulation of methylphenidate (MPH) that utilizes a sophisticated microbead technology composed of two functional film coatings, a delayed-release (DR) and an extended-release (ER) layer, surrounding an immediate-release MPH-loaded core. When administered in the evening, HLD200 is designed to delay the initial release of MPH by approximately 8-10 hours, targeting the onset of clinically meaningful treatment effect upon awakening and throughout the day in patients with attention-deficit/hyperactivity disorder. Two independent phase 1, single-center, single-dose, open-label studies were conducted in healthy adult subjects to investigate the dose proportionality of and the effect of food on HLD200 pharmacokinetics.

Methods: The first study was conducted in two parts: (1) two-way crossover dose proportionality evaluation of a single evening dose of HLD200 at a dose of 20 mg and 100 mg under a fasted state in 20 healthy adults who received a medium-fat breakfast the following morning; and (2) bioavailability assessment of a single evening dose of HLD200 (100 mg) under a fasted state in 13 subjects from part 1 who received a low-fat breakfast the following morning. The second study was a randomized three-way crossover food effect study of HLD200 (100 mg) administered to 18 healthy adults in fasted and fed (high-fat meal) states, and sprinkled on applesauce. In both studies, blood samples were taken over a 48-hour period following dose administration. Adverse events (AEs) were also assessed.

Results: HLD200 demonstrated dose proportionality for Cmax and AUC between the lowest (20 mg) and highest dose (100 mg). Breakfast fat content the morning following evening dosing of HLD200 did not significantly affect the pharmacokinetic profile or parameters (relative Cmax and AUC ratios for low- vs. medium-fat breakfast: 92.3% vs 97.0%). While evening administration of HLD200 with a high-fat meal decreased mean Cmax by 14% (12.2 vs 14.2 ng/mL) and extended Tmax by ~2.5 hours (mean [CV]: 14.3 [11.9%] vs. 16.7 [11.3%] hours; median: 14.0 vs. 16.5 hours) compared with the fasted state, total exposure was equivalent between the fed and fasted states (mean AUC: 175 vs. 180 ng·hr/mL). These food effects were not considered to be of clinical significance. There were no significant differences in Cmax, Tmax, and AUC of HLD200 when sprinkled on applesauce (13.7 ng/mL, 14.6 hours, and 183 ng·hr/mL, respectively) versus the fasted state. In both studies, there were no severe AEs reported and all AEs observed were consistent with those of MPH.

Conclusions: Evening-dosed HLD200 was found to be well-tolerated and demonstrated dose proportionality across the 20-mg to 100-mg dose range. Additionally, the pharmacokinetics of HLD200 were not affected by breakfast fat content the morning following evening dosing or when sprinkled on food, and the differences observed when taken with or without food were not clinically meaningful.

S28. Clinical Response and Symptomatic Remission With MPH-MLR (Methylphenidate Extended-Release) in Children and Adolescents With ADHD

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Background: The MPH-MLR (methylphenidate extended-release) pivotal trial provided evidence of efficacy in children and adolescents with attention-deficit/hyperactivity disorder (ADHD); mean change in ADHD-Rating Scale, 4th edition scores (ADHD-RS-IV) showed significant improvement compared to placebo. Clinical response and symptom remission might be more useful measures of treatment response for clinicians.
Methods: This phase III study was a forced-dose parallel evaluation of MPH-MLR safety/efficacy including 4 phases: screening (≤28 days), 1-week double-blind (placebo or MPH-MLR 10, 15, 20, or 40 mg/day), 11-week open-label dose optimization (11 weeks), and a 21 month compassionate use extension. ADHD-RS-IV scores were obtained at screening and Study Days 0, 7, 14, 21, 28, 56, and 84 and at various points throughout the 21 month extension. In this post-hoc analysis of data from that trial, response was defined as a reduction from baseline in ADHD-RS-IV score ≥30% and symptomatic remission was defined as an ADHD-RS-IV score ≤18 and or a CGI-S≤2 (minimally ill or normal).
Results: A total of 221 patients completed the double-blind phase (MPH-MLR [n=175], placebo [n=46]) and 200 patients completed the 11 week open-label optimization phase. At the end of the 11-week open-label optimization, 94% (188/200) of patients on MPH-MLR responded to treatment and symptomatic remission was achieved in 75% (150/200) with an ADHD-RS-IV score ≤ 18 and 92% (183/200) achieved remission as defined as a CGI-S score ≤2 (minimally or not ill). Throughout the 21 month extension overall response and remission rates were well preserved and maintained by the majority of patients.
Conclusions: Long-term optimized treatment with MPH-MLR achieved high rates of clinical response (94%) and symptomatic remission (75 to 92%) with very low dropout rates due to adverse events. Symptomatic remission was dose related in the initial 1 week fixed dose portion of the trial. The clinical implications of dose-related symptomatic remission and the import of dose optimization for optimal symptomatic improvement should be explored in future clinical trials.

S29. Single-Dose Pharmacokinetics of Amphetamine Extended-Release Oral Suspension (AMPH EROS) Compared With Immediate-Release Mixed Amphetamine Salts

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Background: An amphetamine extended-release oral suspension (AMPH EROS) was developed to address an unmet need for children with attention deficit hyperactivity disorder (ADHD) who require treatment with a long-acting amphetamine but who are unable to swallow tablets or capsules. This single-dose pivotal study evaluated the pharmacokinetics AMPH EROS under fasted and fed conditions, and the relative bioavailability of AMPH EROS compared with immediate-release mixed amphetamine salts (IR MAS) in adults.
Methods: This open-label, randomized, three-period, three-treatment, six-sequence crossover study enrolled healthy men and women volunteers between 18 and 55 years old. Subjects were randomly assigned to receive either 1 dose of AMPH EROS 18.8mg (amphetamine base) under

fed or fasted conditions, or 30 mg of IR MAS (equivalent to 18.8 mg amphetamine base), given as two 15 mg doses four hours apart in the fasted condition. Participants crossed over to alternative treatment regimens with a 7-day washout period between each of the three periods. Eighteen blood samples were collected in each period at pre-dose and at selected time points up to 60 hours post-dosing. Both d-amphetamine and l-amphetamine were measured and PK parameters were calculated for maximum concentration (Cmax), area under the analyte concentration versus time curve (AUC) from time 0 to the time of the last measurable analyte concentration (AUC0-t), and AUC from time 0 to infinity (AUC0-inf) using a non-compartmental approach in SAS® Version 9.3.

Results: Thirty subjects were enrolled and 29 completed the study. Mean Cmax values for AMPH EROS and IR MAS were 54.13 ng/mL and 52.71 ng/mL for d-amphetamine, and 17.29 ng/mL and16.29 ng/mL for l-amphetamine, respectively. Tmax was 4.00 h vs. 6.02 h (d-amphetamine) and 4.00 h vs. 7.00 h (l-amphetamine), respectively. The geometric mean ratios for AUC0-t (d-amphetamine: 106.32%, 90% CI:102.03–110.78; l-amphetamine: 111.35%, 90% CI: 106.22-116.73) and AUCinf (d-amphetamine:105.97%, 90% CI: 101.45-110.70; l-amphetamine: 110.68%, 90% CI: 104.97-116.70) were within the 90% confidence limits (80.0%-125.0%) for bioequivalence. The peak exposure under fed conditions compared to fasting conditions as the ratio of geometric means for Cmax was 101.85% for d-amphetamine and 102.39% for l-amphetamine, and overall exposure for AUC0-t and AUCinf was 94.62% and 94.33% (d-amphetamine) and 93.28% and 92.64% (l-amphetamine), respectively. The Tmax was 5.00h for the fed condition versus 4 h for fasting, for both d- and l-amphetamine. No serious adverse events were reported during the conduct of this study. Both the AMPH EROS and IR MAS formulations were generally well tolerated by study participants.

Conclusions: The bioavailability of a single dose of AMPH EROS (18.8 mg amphetamine base) was comparable to two 15 mg doses of IR MAS (equivalent to 18.8 mg amphetamine base, total dose), given 4 hours apart, based on AUC. AMPH EROS (both d- and l-amphetamine) showed equivalent peak and overall exposure to IR MAS as the 90% confidence intervals about the ratio of geometric means were within 80.00-125.00% for AUCt, AUCinf and Cmax. There was no food effect observed for AMPH EROS. All AEs were mild in intensity and both treatments were well tolerated.

S30. Efficacy and Safety of Modified-Release Methylphenidate in Adults With Attention-Deficit/Hyperactivity Disorder in Routine Clinical Care: Results: From the Idea Study

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Background: A modified-release methylphenidate (MPH-MR) proprietary product has been approved as the first drug for the treatment of adults with attention-deficit/hyperactivity disorder (ADHD) in Germany in 2011. However, data on efficacy and tolerability of MPH-MR in the routine care setting in adults are scarce. Here we present results of a non-interventional study related to efficacy and safety of the use of MPH-MR in the treatment of adults with newly diagnosed ADHD in routine care.

Methods: The prospective, non-interventional cohort study IDEA was conducted from Sept 2012–March 2014 in Germany. Adults with newly diagnosed ADHD according to the validated, DSM-

IV-based IDA scales (Integrated Diagnosis of ADHD) were assigned to treatment with MPH-MR for 12-14 weeks. Primary outcome was efficacy based on Clinical-Global-Impression (CGI). Secondary outcome measures included patient-reported data (Wender-Reimherr-Self-Report-Scale – WR-SRS), safety, tolerability, and dosage.

Results: Patient characteristics: 468 adult ADHD patients (mean age (±SD) 32.5±10.8 years) in 126 outpatient centres were included, 57.9% were male. The majority of patients were diagnosed with combined type (44.7%) or primarily inattentive type (34.6%) ADHD. Psychiatric comorbid conditions were common (42.1%), primarily depression (27.6%). Median MPH-MR dose at the end of the study was 40.0 mg MPH-MR/day (range 5.0-80.0 mg/day). Concurrent medication (primarily antidepressants) was prescribed in 35.3% of all patients. A total of 21.8% of patients additionally received non-pharmacological interventions (primarily psycho- and behavioural therapy). CGI-Severity-Scale: Severity of disease improved from baseline to 3.0 months (median, range 0.4-18.6 months): 0.5% vs. 0.2% extremely ill, 13.8% vs. 4.8% severely ill, 52.1% vs. 20.2% markedly ill, 26.8% vs. 32.6% moderately ill, 5.7% vs. 31.2% mildly ill, 0.7% vs. 7.1% borderline cases, 0.5% vs. 3.9% not ill. CGI-Improvement-Scale: 74.5% of patients were assessed as responders, defined as much and very much improvement in patient's status. CGI-Efficacy-Index: Therapeutic efficacy was rated very good, moderate, minimal and unchanged to worse for 40.9%, 42.1%, 14.4% and 2.6% of patients. Patient-reported WR-SRS: A significant ($p<0,001$) improvement from baseline to end of the study was reported for impairments related to attention difficulties (-30%), impulsivity (-23%), hyperactivity/restlessness (-23%), temper (-22%), affective lability (-23%), disorganization (-23%), oppositional behaviour (-20%), academic problems (-18%) and social adjustment (-17%). Safety: 10.9% of patients experienced a total of 100 adverse events. Reduced appetite and headache were reported most frequently. One incident was considered serious (polytoxicomania relapse), but with no clear association to the MPH-MR treatment. Changes in blood pressure and heart rate were only minor and considered clinically irrelevant.

Conclusions: MPH-MR is effective and well tolerated in outpatient routine clinical care in adults with ADHD. Clinically relevant improvements in expert and patient ratings were recorded for core symptoms of ADHD, but also for related functional parameters after a median treatment period of 3 months. The IDEA study confirms that results from controlled clinical trials may well be transferred into routine care settings.