



**APSARD**  
**2019** ANNUAL  
MEETING  
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# **2019 APSARD Annual Meeting**

## **Abstract Book**

**January 18-20, 2019**  
**The Washington Marriott Wardman Park**  
**Washington, D.C., USA**

**APSARD**

The American Professional Society  
of ADHD and Related Disorders



# Friday, January 18, 2019

## Welcome and Opening Plenary

5:30 p.m. - 7:30 p.m.

### 1. NEW PERSPECTIVES ON IMPULSIVE CHOICE IN ADHD: REFINING THE PHENOTYPE AND AUGMENTING THERAPEUTIC OPTIONS

**Chair:** Jeffrey Newcorn, Mount Sinai Medical Center

**Overall Abstract:** This session will present new perspectives on the science surrounding impulsive choosing and impulsive behavior in ADHD, and then consider implications for pharmacological treatment. Edmund Sonuga-Barke will first consider the issue of impulsive choice (i.e., preference for smaller, immediate vs larger, delayed rewards) in the context of motivational deficits in ADHD. He will examine the neuroscience of impulsive choice and present data implicating the limbic and default mode systems in regulating this phenomenon. He will then build a model that provides an integrative view of impulsive choice in ADHD and highlight different ways to interface with the underlying neural systems. Next, David Coghill will examine evidence supporting the complex relationship of impulsivity to ADHD, considering the various models of impulsivity that have been proposed. He will highlight the multiplicity of pathways into impulsivity, and likely different clinical presentations associated with each. He will specifically consider the relationship between cognitive and behavioral impulsivity, and present data regarding pharmacologic treatment in relation to each.

#### **Learning Objectives:**

- Understand the central relevance of impulsive choice and delay aversion to ADHD.
- Understand the neurobiology underlying impulsive choice and delay aversion in ADHD.
- Appreciate pharmacologic approaches to the treatment of impulsive choice and delay aversion in ADHD.

### 1.1 WHY ARE WE (NOT) WAITING? NEW PERSPECTIVES ON THE NEUROSCIENCE OF IMPULSIVE CHOICE IN ADHD

Edmund Sonuga-Barke, King's College London

**Abstract:** The apparently economically irrational choice of small immediate over large delayed rewards is a core feature of the motivational signature of ADHD. However, a definitive understanding of the underlying pathophysiology of this impulsive choice remains elusive. In this talk I will explore new perspectives on impulsive choice that take us beyond the “usual suspects” of executive dysfunction and altered reward processing. The talk will have four sections. In section 1, I will briefly describe neuroscience driven changes in our understanding of ADHD pathophysiology focusing on the concepts of complexity and heterogeneity. In section 2, evidence that impulsive choice is a defining feature of the motivational phenotype of ADHD will be presented. In section 3, I will provide experimental evidence for a role for altered limbic and default mode system function in impulsive choice in ADHD. Finally, I will present an integrative multi-system model of sub-optimal decision making in ADHD that may provide the basis of an explanation of impulsive choice.

### 1.2 PILLS, SKILLS AND BEHAVIOURS: EXPLORING THE PSYCHOPHARMACOLOGY OF IMPULSIVITY

David Coghill, University of Melbourne

**Abstract:** Impulsivity comes in many colours. Whilst these often look the same on a casual, or even clinical, examination, they actually arise from very different sources. At the turn of the century Russel Barkley's unified theory for ADHD proposed that deficits in inhibitory control were the core cognitive deficit underpinning ADHD. Although it is clear that this is not the case impulsivity and failures of inhibition sit alongside, and perhaps intertwined with, the other key cognitive deficits associated with ADHD. Pharmacological treatments for ADHD have been demonstrated to reduce impulsivity at a number of levels. Clearly these medications are all effective at improving the hyperactive/impulsive symptoms of ADHD. Although in our clinical experience we have questioned whether they are actually more effective at reducing hyperactivity than impulsivity. At the cognitive level they improve inhibitory control, and this may have a knock on effect on other cognitive domains. It is however now clear that the effects on memory and other aspects of cognition are not secondary to those on inhibitory control. This talk will explore the literature pertaining to these findings consider some other issues relating to control of affect and emotions in ADHD and look at some newer findings relating to the impact of medications on the default mode network and decision making.

## Saturday, January 19, 2019

### Plenary Session

9:00 a.m. - 11:00 a.m.

### 2. THE RELEVANCE OF BIOLOGICAL AND ENVIRONMENTAL RISK FACTORS IN THE ADHD

**Chair:** J.J. Sandra Kooij, The Hague, The Netherlands

**Overall Abstract:** In this symposium the current state of knowledge on biological and environmental risk factors in ADHD will be discussed, varying from genetics to biomarkers, and from cognitive and physiological measures to comorbidity, and to catecholamines and function of the Prefrontal Cortex.

#### Learning Objectives:

- Being updated on the role of cognitive and physiological measures in the pathophysiology of ADHD.
- Learning about the interaction between the Prefrontal Cortex and catecholaminergic activity such as dopaminergic and noradrenergic mechanisms, in relation to medications used in ADHD.

### 2.1 CATECHOLAMINE REGULATION OF PREFRONTAL CORTEX: RELEVANCE TO ETIOLOGY AND TREATMENT OF ADHD

Amy Arnsten, Yale School of Medicine

**Abstract:** ADHD involves dysfunction of the prefrontal cortex (PFC), which normally serves to provide top-down regulation of attention and impulse control. The PFC is powerfully modulated by catecholamines, where dopamine D1R, and noradrenergic alpha-2A-AR mechanisms are needed for network connectivity and function, but excessive catecholamine actions, e.g. due to stress or excessive stimulant dose, can impair PFC function. These

mechanisms are now understood at the ionic level and will be described. All currently approved medications for ADHD act through these receptors, and likely have many therapeutic effects through actions in PFC.

## **2.2 USING GENETICS TO EVALUATE ENVIRONMENTS AND ENDOPHENOTYPES FOR ADHD**

Joel Nigg, Oregon Health and Science University

**Abstract:** Two lines of work in ADHD can be advanced by capitalizing on recent genetic data. First, a key goal for the field has been to determine if cognitive and physiological measures proposed as endophenotypes are in fact part of the pathophysiology of ADHD. Here, the use of polygenic risk scores from molecular genetic data enables a direct test of whether common genetic liability for ADHD or other disorders is statistically explained by genetic effects on cognitive measures like working memory or response inhibition, as well as on cognitive measures like MRI or psychophysiological metrics. Second, numerous environmental risk factors for ADHD are known, but it has been unclear whether they are causal. The use of a molecular genetic design with Mendelian randomization provides some purchase on this question. This talk illustrates both approaches with recent discoveries in ADHD. Finally, the talk asks whether peripheral blood biomarkers can be used to index environmental risk for ADHD using the example of cytokines and inflammation.

## **2.3 COMORBIDITY OF ATTENTION DEFICIT DISORDER AND PHYSICAL CONDITIONS: EXPLANATIONS AND IMPACT**

Kathleen Merikangas, NIH/NIMH

**Abstract:** Systematic reviews of specific physical and/or mental disorders, as well as studies of clinical and community samples, have documented the co-occurrence and consequences of comorbidity in youth. However, much of the current evidence is based on cross-sectional assessment of small numbers of cases and self-reported disorders rather than systematic diagnostic assessments.

This article examines patterns of comorbidity of Attention Deficit Hyperactivity Disorder (ADHD) and comprehensive range of physical conditions in several large community surveys of youth including the Philadelphia Neurodevelopmental Cohort Study (PNC), the National Comorbidity Survey Adolescent Supplement (NCS-A), the Ontario Child Health Survey (OCHS), and the Healthy Brain Network (HBN). Across all studies, there were consistent associations between ADHD with other neurodevelopmental and neurologic conditions. ADHD was also associated with allergies and asthma, and gastrointestinal symptoms and disorders in numerous studies.

Potential mechanisms for these associations are described, and data from family/genetic studies and prospective research are used to examine these explanations. The influence on physical disorder comorbidity on the impact and treatment of ADHD is also described. This work highlights the importance of comprehensive evaluation of youth with ADHD.

**Lifetime Achievement Plenary**

**11:30 a.m. - 12:30 p.m.**

## **3. LIFETIME ACHIEVEMENT PLENARY**

**Chair:** Joseph Biederman, Massachusetts General Hospital

**Overall Abstract:** The 2019 Lifetime Achievement Award is presented to Professor Martha Denckla. This award recognizes Professor Denckla's extraordinary dedication to the field of ADHD and her contribution to support the science of ADHD and its treatment. Professor Denckla's work focused on the intersection between ADHD, learning disabilities, and executive dysfunction. Her work contributed to advances in the neuropsychological assessment of children, which led to neuroimaging research enhancing the understanding of executive dysfunction in ADHD.

**Learning Objectives:**

- To provide an overview of Dr. Denckla's contributions to the field of ADHD.
- To provide an overview on how insights in the understanding of executive dysfunctions advanced the field of ADHD.

### **3.1 FROM LD TO ADHD, AN UNEXPECTED JOURNEY**

Martha Denckla, Kennedy Krieger Institute/ Neurology at Johns Hopkins University School of Medicine

**Abstract:** Taking an autobiographical approach, this review spans the years 1969-2019, tracing my journey from cognitive/behavioral neurology into Learning Disabilities (LD, highlighting dyslexia) through Minimal Brain Dysfunction (MBD) to ADHD. Both research and clinical motivations and experiences culminated in a focus on executive function/dysfunction, with advances in neuromotor and neuropsychological assessments, many kinds of magnetic resonance imaging (anatomical, functional, diffusion-weighted, and connectivity analysis) enhancing understanding of executive dysfunction as a factor mediating the LD/ADHD association. A "side journey" into the LD/ADHD aspects of two genetic disorders (Tourette Syndrome and Neurofibromatosis-1) proved enlightening and enriching of that understanding. The emphasis will be on the diagnostic overlap zone linking neurology, neuropsychology, and psychiatry and implications for the non-pharmacological components of multimodal treatment programs for ADHD.

#### **Concurrent Symposia Sessions**

**2:30 p.m. - 4:30 p.m.**

### **4. RISK FACTORS AND TREATMENT OF ADHD AND SUBSTANCE USE DISORDERS: FROM SCIENCE TO CLINICAL PRACTICE**

**Chair:** Frances Levin, Columbia University Medical Center

**Overall Abstract:** Clinicians are often faced with the complexity of assessing and treating adults with ADHD and substance use disorders. Problems of impulse control and early social and environmental factors are crucial in the initiation and maintenance of substance use. Dr. Dougherty will present data demonstrating how pre-adolescent impulse control predicts later substance use and how substance use impacts on the trajectory of impulse control which may, in turn, increase the risk of further substance use involvement. Factors that impact on risk and resiliency will be discussed. Dr. Wilens will then present data from cross-sectional, longitudinal, epidemiological and translational studies of non-medical use of prescription ADHD stimulants in college-aged youth. He will highlight the high rates of stimulant misuse in college settings, short and long-term consequences of use as well as the over-representation of psychiatric comorbidities (e.g., depression, substance use disorders) in stimulant misusers. For individuals diagnosed with both ADHD and a substance use disorder, treatment can be

challenging. Two specific groups of interest are those with cannabis use disorders and opioid use disorders. Dr. Yule will provide some background on the opioid epidemic and discuss the clinical challenges in managing individuals with ADHD and opioid use disorders. Dr. Gray will focus the over-representation of cannabis use disorders among those with ADHD. Behavioral and pharmacologic advances in the treatment of cannabis use disorder will be provided as well as practical considerations in working with individuals presenting with both ADHD and cannabis use disorder.

**Learning Objectives:**

- To become knowledgeable about the risk factors in childhood associated with substance use along with stimulant misuse in college aged youth.
- To learn about the clinical challenges in the management of ADHD and OUD in intensive SUD treatment programs.
- To become knowledgeable about the recent advances in behavioral and pharmacological treatments for CUD in youth and the clinical consideration for individuals presenting with co-occurring CUD and ADHD.

**4.1 ADOLESCENT DEVELOPMENTAL TRAJECTORIES OF IMPULSE CONTROL AND SENSATION SEEKING AND RISK FACTORS RELATED TO SUBSTANCE USE**

Donald Dougherty, UT Health

**Abstract:** Data will be presented that has been collected from a longitudinal study of adolescents at high-risk for developing substance use disorders. The initial aims of this study were to determine how preadolescent impulse control at study entry (ages 10-12) predicts later substance use and later how substance use involvement alters developmental trajectories of impulse control. Recent analyses has focused on applying the Dual Systems model of adolescent risk taking by addressing whether processes in the model are independent or interdependent, how they develop in non-normative samples to explain problematic patterns of substance use, and whether processes in the model are affected by social/environmental factors related to risk and resiliency.

**4.2 ADHD AND OPIOID USE DISORDERS: HOW TO BEST INTERVENE**

Amy Yule, Harvard Medical School/Massachusetts General Hospital

**Abstract:** This presentation will provide background on the opioid epidemic in the United States, and review evidence-based treatments for opioid use disorders (OUD). Studies examining the prevalence of co-occurring ADHD and OUD and the impact of ADHD treatment in this population will also be reviewed. Finally, clinical challenges in the management of ADHD and OUD in intensive SUD treatment programs will be discussed.

**4.3 ADHD-STIMULANT MEDICATION MISUSE: WHAT IS REALLY GOING ON?**

Timothy Wilens, Massachusetts General Hospital

**Abstract:** The nonmedical use (NMU) of stimulants (misuse) in college aged youth remains of utmost public health and clinical concern. The objective of this presentation is to evaluate comprehensively the literature attending to the prevalence, routes, comorbidity, consequences, and shorter- and longer-term outcomes of young people with NMU of stimulants.

The data presented are selected from cross-sectional, longitudinal, epidemiological, and translational studies of the NMU of prescription ADHD stimulants in college- aged youth. Excluded were misuse of non-prescription stimulants (not including cocaine,



methamphetamine). Data were derived from survey, structured interview, objective measures, dopamine binding characteristics, and self-report questionnaires.

A number of studies emerged highlighting the high prevalence of NMU of stimulants in college settings. The majority of NMU was with the immediate-release as opposed to extended-release preparations and was used most commonly for performance enhancement reasons. While stimulants were generally taken orally during times of misuse, intranasal misuse was noted in a substantial minority of misusers. Comorbidity with ADHD, mood, and substance use disorders; as well as executive dysfunction was overrepresented in stimulant misusers. Consequences to stimulant misuse were noted both short and long term.

Our data suggest that college students who misuse stimulant medications are at very high risk for concomitant psychopathology and substance use disorders, as well as shorter- and longer-term adverse outcomes.

#### **4.4 ADHD AND CANNABIS USE DISORDERS: ADDRESSING THE COMORBIDITY**

Kevin Gray, Medical University of South Carolina

**Abstract** Cannabis Use Disorder (CUD) is common among adolescents and young adults, and co-occurring Attention-Deficit/Hyperactivity Disorder (ADHD) may complicate the presentation, course, and treatment of CUD. This presentation will highlight recent advances in behavioral and pharmacological treatments for CUD in youth and highlight clinical considerations for individuals presenting with co-occurring CUD and ADHD.

#### **5. BENEFITS AND CHALLENGES OF PSYCHOSOCIAL TREATMENT IN ADHD**

**Chair:** Russell Barkley, Virginia Commonwealth University Medical Center

**Overall Abstract:** A number of approaches to the psychosocial management of ADHD in children and adults have sufficient scientific evidence supporting their effectiveness that they can be considered evidence-based therapies for the disorder. Lacking in this extensive body of research is any widespread or longstanding interest in documenting the adverse events or side effects that may be associated with these interventions. Yet research in psychotherapy and behavioral therapies for the past 50 years has shown that such adverse events are likely to occur, even if in a minority of cases. Based on two special issues of the ADHD Report (February, March 2018) that focused on the side effects of the eight most evidence-based approaches to management of ADHD, this symposium will review the three most commonly used and science-based psychosocial treatments for child and adult ADHD: parent and family behavior management training for child and adolescent ADHD, classroom behavior management for child and adolescent ADHD, and cognitive behavior therapy for adults with ADHD. Each presenter will note the effectiveness of each intervention and their continuing promise for assisting in the management of the disorder. Yet each presenter will also review the various adverse events that have been documented in research or witnessed in their own implementation of these therapies in their research studies on them. The symposium is designed to encourage a means for conceptualizing these events, more frequent and widespread monitoring and identification of adverse events associated with these therapies, as well as the development of more standardized measures for doing so, similar to what is commonplace in research on ADHD medications.

##### **Learning Objectives:**

- Promote understanding of the effectiveness of three major evidence-based psychosocial treatments for ADHD in youth and adults.
- Increase awareness of the nature of and risk for adverse events in parent training and family management.

- Advance understanding of the nature of and risk for adverse events in classroom behavioral management of ADHD.
- Further understanding of the nature of and risk for unwanted or side effects of cognitive behavioral therapy for adults with ADHD.

### **5.1 CLASSROOM BEHAVIOR MANAGEMENT OF ADHD YOUTH**

Linda Pfiffner, University of California - San Francisco

**Abstract:** Classroom behavioral interventions have a long-standing evidence base to support use with students having ADHD. Moderate to large treatment effects are found on inattentive and disruptive behavior and small to moderate effects on academic functioning (DuPaul, Eckert, & Vilaro, 2012; Fabiano et al., 2009). Despite these salutary effects, behavioral strategies may be associated with adverse side-effects. Adverse effects can be a result of the strategies not being delivered in a manner consistent with empirical research. Unfortunately, scant empirical attention has been paid to the possibility of side-effects when strategies are delivered in accordance with empirical recommendations. Based on the limited research and on clinical experience, this presentation will cover possible adverse side-effects of classroom behavioral interventions including possible side-effects for students with ADHD who are targeted for treatment, and possible negative impacts on their classmates and teachers. Recommendations will be provided for future studies of classroom behavioral intervention as well as guidelines for clinicians to consider in monitoring and preventing adverse side-effects.

### **5.2 EFFECTS AND SIDE EFFECTS OF COGNITIVE-BEHAVIORAL THERAPY FOR ADULT ADHD**

Laura Knouse, University of Richmond

**Abstract:** The presentation will briefly review current evidence for the efficacy of CBT for adults with ADHD and will discuss potential side effects of this form of treatment. Clinical recommendations for anticipating and addressing side effects during treatment will be offered along with recommendations for improving research on CBT side effects.

## **Sunday, January 20, 2019**

### **Plenary Session**

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

### **6. GENETICS OF ADHD AND IMPLICATIONS FOR EDUCATING PATIENTS AND MANAGING THE DISORDER**

**Chair:** Russell Schachar, University of Toronto

**Overall Abstract:** Our understanding of ADHD is being radically transformed by rapidly accumulating genetic information that addresses key questions. This plenary will provide an update on the implications of modern genetics for our understanding of ADHD. Is ADHD best understood as a disorder or trait? Why do people with this diagnosis have increased risk of other mental and medical conditions? Can genetic testing be used to predict response to currently available treatments and help us find new ones?



### **Learning Objectives:**

- Learn what recent genetic research tells us about the nature of ADHD.
- Discuss genetic explanations for comorbidity of ADHD, mental and medical illnesses.
- Become familiar with the usefulness of genetic testing for predicting drug response in ADHD.

## **6.1 WHAT ARE THE BOUNDARIES OF ADHD? A GENOMIC PERSPECTIVE**

Stephen Faraone, SUNY Upstate Medical University

**Abstract:** The last five years has witnessed an exponential growth in knowledge about the genetics of ADHD and comorbid disorders. This work has identified specific genetic loci that increase the risk for these disorders and also shows that most psychiatric disorders have a polygenic origin. This talk reviews these data and presents molecular genetic evidence that confirms results from epidemiologic studies by showing a molecular genetic overlap between ADHD and many of its comorbid disorders. It also presents new data indicating genetic overlap with schizophrenia, with behavioral/cognitive trait and with somatic comorbidities such as obesity. Also reviewed is ADHD's genetic overlap with neurologic disorders. After summarizing these data and presenting new data on the overlap between genetic and structural MRI assessments of comorbidity, implications for the structure of psychopathology are discussed along with clinical implications for diagnosis and the use of pharmacogenomics.

## **6.2 PHARMACOGENOMIC MARKER DISCOVERY AND DELIVERY OF OPTIMIZED MEDICATION TREATMENT GUIDANCE TO IMPROVE CARE IN CHILD AND ADULT PSYCHIATRIC DISORDERS**

James Kennedy, Centre for Addiction and Mental Health, University of Toronto

**Abstract:** Pharmacogenomic (PGx) discovery and application can predict response and the risk for side effects with specific medications. The field of psychiatry is in the unique position to gain greatly from the use of PGx testing. Three principles of PGx include discovery of markers, validation of markers predicting side effects and outcomes, and clinical utilization of PGx testing. The current overall status of clinical PGx testing, including pros and cons, will be reviewed. In general, there is a need for high quality studies in this area. In ADHD, PGx studies of stimulants have shown very mixed results. Atomoxetine blood levels appear to be predicted by CYP2D6 gene variants. Our discovery of new markers to predict response in adults and children include a panel of 6 primarily hypothalamic expressed genes for antipsychotic-induced weight gain, as well as preliminary gene panels for tardive dyskinesia (DRD2, DRD3, VMAT2) and overall psychotropic response (CYPP450 system, DRD2, 5HT2A, 5HTT, other genes). Our large (n = 11,000) open label IMPACT trial evaluated PGx test guidance of prescribing antidepressants and antipsychotics in academic and community clinical settings in the Toronto area. Inclusion criteria were broad: intent to start, or to change, psychotropic medication in patients aged 7 to 85 years. The number of patients less than age 18 was n = 1,400. Patient outcomes were measured at baseline, 4 and 8 wks. In a subset of n = 2,000 from the IMPACT study, patients who switched to more genetically congruent medications had significantly greater improvement in response (p=0.03), and remission (p<0.008) compared to patients who remained on incongruent medications. Of considerable interest, patients whose treatment was guided by PGx testing in primary care saw significantly greater symptom improvement compared to patients tested under the care of psychiatrists (p<0.0005) resulting in 1.4 and 1.7 greater odds of response and remission in primary care compared to psychiatric settings, respectively (p<0.005).

The development of PGx testing in psychiatry, and particularly in children and adolescents, is at an early stage of development, however the increasing number of clinical trials is overall producing very promising results.

## **Plenary Session**

**11:00 a.m. - 12:30 p.m.**

### **7. RELEVANCE OF IMAGING IN UNDERSTANDING ADHD**

**Chair:** Philip Asherson, Kings College London

**Overall Abstract:** Neuroimaging studies have opened up new avenues for investigating the structural and functional underpinnings of attention-deficit/hyperactivity disorder (ADHD) and other neurodevelopmental conditions such as autism spectrum disorder (ASD). Multiple cognitive and neural deficits are seen in neurodevelopmental disorders compared to healthy controls, although none have been found to be sufficiently sensitive or specific to be used for diagnostic testing. Another limitation is that current studies do not yet clarify the causal role of the observed deficits: which could reflect genetically correlated neural and cognitive deficits (risk liability markers), or intermediate endophenotypes on the pathway from genes to neurodevelopmental phenotypes.

In this symposium we will tackle two key questions. First, to what extent are there similarities or differences in the neuroimaging markers of ADHD and ASD? In general, a consensus has been found that there are considerable differences in the neural and cognitive deficits associated with each disorder, particularly when examined in well characterized clinical samples that separate out the two disorders. Second, we examine the neural correlates of persistence and remission when children with ADHD are followed into young adulthood. Here we find that while some neuroimaging markers are seen in both persisters and remitters, and therefore appear to play no direct role in the adult ADHD phenotypes; other neuroimaging markers are only seen in persistent cases of ADHD and might therefore reflect core processes linked to the symptoms of ADHD in adults. Longitudinal follow-up studies have huge potential to highlight the best targets for treatment.

#### **Learning Objectives:**

- Learn neuroimaging similarities and differences in ADHD and ASD.
- Learn neuroimaging similarities and differences between persistent and remitted cases of ADHD in young adulthood.
- Learn the causal role of associated neuroimaging findings.

#### **7.1 DO ADHD AND AUTISM OVERLAP IN THE BRAIN CONNECTOME? INSIGHTS FROM NEUROIMAGING**

Adriana Di Martino, The Child Mind Institute

**Abstract:** Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are distinct neurodevelopmental conditions that often present with overlapping, that cause impairment and challenge diagnosis and care. While their co-occurrence has been increasingly recognized, the extent to which ADHD and ASD have similar neural underpinnings remain, to date, unclear. Neuroimaging techniques are promising approaches for non-invasively investigating the brain organization of these neurodevelopmental conditions and initial results have suggested they both affect the brain functional connectome. But only a few studies have compared these conditions directly or focused investigations on their

comorbidity. After a review of this emerging literature, novel empirical data examining the extent of overlap between these conditions will be presented and their clinical and research implications discussed.

## **7.2 GROWING OUT OF ADHD: INSIGHTS FROM MULTIMODAL IMAGING**

Philip Shaw, National Human Genome Research Institute

**Abstract:** Why do some children ‘grow out’ of ADHD, showing variable degrees of remission from the disorder, whereas others have symptoms that persist into adulthood? Is remission due to the emergence of compensatory processes underpinned by neural re-organization? Or is remission due to the ‘normalization’ of early, childhood transient anomalies in brain structure and function?

To address this question, we followed a cohort of children with and without ADHD into adulthood. We contrasted the young adults with persistent ADHD against those showing remission and never affected individuals. White matter tract (diffusion tensor imaging) and multimodal functional imaging (fMRI and magnetoencephalography-MEG) were acquired at this adult endpoint.

We found that young adults whose ADHD had persisted from childhood show atypical neural features, whereas remitters did not differ from those who were never affected. This pattern held for white matter microstructure and intrinsic functional connectivity (defined through task free fMRI and MEG). Further, during a probe of motor inhibition, a core deficit in the disorder, we found that remitters showed typical hemodynamic and electrophysiological activity at both cortical and cerebellar levels. Functional anomalies were detected in the caudate in all adult subjects with a childhood history of ADHD, regardless of adult outcome.

Combined, the findings suggest that remission might be aligned to processes that may partly ‘normalize’ early anomalies in cerebral cortical structure and function, rather than the emergence of compensatory strategies and neural reorganization. Anomalies of striatal function may reflect a childhood history of ADHD, regardless of adult outcome. Future studies will further test these models or remission using prospectively acquired multimodal imaging data.

### **Concurrent Symposia Sessions**

**2:30 p.m. - 4:30 p.m.**

## **8. SEIZURES, TICS, AND OCD IN ADHD: IMPACT ON MANAGEMENT**

Steven Pliszka, UT Health Science Center at San Antonio

**Overall Abstract:** Tics, OCD and seizures occupy a boundary between neurology and psychiatry. Each present clinical challenges when they are comorbid with ADHD. This symposium will present recent findings and advice for clinical management for each of these presentations. Dr. Coffey will examine issues regarding tics in ADHD, including the overlapping neurobiology between ADHD and tic disorders in both genetic and neuroimaging studies. She will present current thinking on both the pharmacological and psychosocial treatment of tics in the presence of ADHD in order to optimize treatment of both disorders. Dr. Gonzalez-Heydrich will speak on the bidirectional interface of epilepsy and ADHD. ADHD often precedes and increases risk for epilepsy arguing for an underlying vulnerability to both in many patients. Genetic and environmental insults to the mechanisms of neurodevelopment

that can lead to weakness of executive circuitry and cause ADHD, increase risk of epilepsy, and lead to comorbid ADHD and epilepsy. Rare genetic syndromes associated with ADHD, epilepsy and combined ADHD & epilepsy, point to these neuropathological mechanisms. He will describe how ADHD is undertreated in those with epilepsy due to unreasonable fears of the effects of ADHD medications on seizures and discuss the effects of anti-epileptic drugs (AEDs) on attention. In addition, Dr. Daniel Geller will examine the comorbidity of OCD and ADHD, presenting data from a large cohort (n=121) of ADHD patients with and without OCD. This study suggests that when ADHD-like symptoms are seen in OCD youth they reflect a true comorbid state of OCD plus ADHD and that the ADHD syndrome may be independent of OCD in comorbid youth. Attention to both disorders is needed to assure best clinical outcomes.

### **Learning Objectives:**

- Understanding the overlapping neurobiology of tics and ADHD.
- Discuss the genetic and environmental risk factors that may interact in patient with both epilepsy and ADHD.
- Discuss the effects of anti-epileptic drugs on cognition and understand the risk/benefits of the use of ADHD medications in patient with epilepsy.
- Understand the nature of the comorbidity of OCD and ADHD and its implication for the treatment of both disorders.

## **8.1 ADHD AND TICS: BOUNDARIES, OVERLAP AND DISENTANGLEMENT**

Barbara Coffey, University of Miami Miller School of Medicine

**Abstract:** Bidirectional overlap between Attention-Deficit/Hyperactivity Disorder (ADHD) and tic disorders has long been described. Twenty percent of individuals with ADHD may meet diagnostic criteria for a tic disorder, and the prevalence of ADHD in individuals with Tourette's Disorder (TD) is reported to be as high as 50-60 percent. While comorbid presentation of ADHD and tic disorders is firmly established, underlying genetic and pathophysiologic mechanisms remain elusive. Neurobiological studies may serve as a foundation for understanding similarities and differences in clinical phenomenology between ADHD and tic disorders and inform treatment.

Overlapping network alterations in pathophysiology of ADHD and comorbid TD have been reported in the cortico-striatothalamo-cortical circuit (CTSC), associated with tic generation, and in impulsivity and executive dysfunction characteristic of ADHD. Functional MRI findings in adolescents with TD have reported immature brain networks, validating the concept of tic disorders as neurodevelopmental disorders. Reductions in total cerebral volume, prefrontal cortex, basal ganglia, dorsal anterior cingulate cortex, corpus callosum, and cerebellum reported in ADHD patients are consistent with fronto-striatal models of ADHD. Structural MRI findings have revealed that individuals with TD and comorbid ADHD have smaller caudate nuclei. Some studies have suggested involvement of basal ganglia circuits, composed of a direct (excitatory) pathway facilitating cortically mediated behaviors, and an indirect (inhibitory) pathway inhibiting conflicting behaviors. An under-functioning direct pathway may result in interrupted behaviors (problems with sustaining attention and impulsivity) characteristic of ADHD, whereas disruption of the indirect pathway may cause repetitive behaviors and thoughts, such as those in association with TD and/obsessive compulsive disorder.

Imaging studies have revealed both similarities and differences between ADHD and tic disorders; for example, some studies demonstrated a reduction in right cerebral volume, right caudate nucleus, and cerebellum in ADHD, whereas in TD, only reduced volume of caudate

nucleus has been shown. On the other hand, significant loss of normal globus pallidus asymmetry has been reported in both ADHD and TD patients.

Genetic studies have also reported similarities and differences in the relationship between tic disorders and ADHD. In one study, co-existing ADHD plus TD in Tourette's patients increased the risk of both comorbid ADHD plus TD and TD in the siblings of these index patients. These findings were consistent with those of a previous study which found no increase in rates of ADHD among parents of probands with TD compared with controls, suggesting that these disorders segregate independently from TD.

With regard to course, ADHD symptoms usually precede onset of tics. Especially if motoric hyperactivity and restlessness are present, tics may be overlooked, or assumed to be part of ADHD clinical phenomenology. Comorbidity confers a more difficult clinical course and outcome for both ADHD and Tourette's Disorder. ADHD typically interferes more with overall functioning than tics; it has been clearly demonstrated that ADHD leads to greater disability than tic disorders or Tourette's Disorder alone. Comprehensive and systematic evaluation of both ADHD and tic symptoms is necessary to determine relative contribution of each type of symptoms to the patient's distress, functional impairment and quality of life.

Optimal patient outcomes may depend on management of both ADHD symptoms and tics when they co-occur. Research in the past decade has shown that these conditions can be safely treated simultaneously. Treatment is based on a consideration of the impact of tics, in the context of ADHD, on social, emotional, family, and academic/occupational functioning. If tics are not causing significant distress or impairment, treatment may not be necessary. Treatment is indicated when tics cause distress or impairment. In general, as ADHD is more likely to be associated with both short term and, left untreated, longer-term poor outcomes, treatment of these symptoms should be prioritized.

In summary, ADHD and tics, both neurodevelopmental disorders, commonly co-occur; symptoms frequently overlap and are difficult to disentangle. Cortico-striato-thalamo-cortical circuit (CTSC) disinhibition appears to underlie both disorders, with significant basal ganglia contribution in Tourette's Disorder, and frontal-striatal in ADHD. A systematic approach to evaluation of patients with ADHD and tic disorders is necessary, so as to appropriately prioritize symptoms for treatment.

## **8.2 EPILEPSY AND PSYCHIATRIC DISORDERS: BIDIRECTIONAL INTERFACE AND OPPORTUNITY**

Joseph Gonzalez-Heydrich, Boston Children's Hospital

**Abstract:** Epilepsy's association with ADHD symptoms arises at many levels:

1) ADHD often precedes and increases risk for epilepsy arguing for an underlying vulnerability to both in many patients. Genetic and environmental insults to the mechanisms of neurodevelopment that can lead to weakness of executive circuitry and cause ADHD, increase risk of epilepsy, and lead to comorbid ADHD and epilepsy. Rare genetic syndromes associated with ADHD, epilepsy and combined ADHD & epilepsy point to these neuropathological mechanisms. Many of these mechanisms are involved in early brain development and include neuronal migration, synaptic formation/remodeling/maintenance and balance of inhibition and excitation. Such genetic syndromes can provide models for understanding the common pathogenic pathways leading to ADHD and epilepsy and offer the potential for translating

information these mechanisms into new treatments that may prevent both ADHD and epilepsy in patients with these disorders and also in patients with milder defects in the same pathways.

2) Inter-ictal network effects of epileptiform lesions, discharges and seizures can cause ADHD symptoms. For example, executive function in patients with idiopathic generalized epilepsy is impaired and is further impaired if these patients also have interictal epileptiform discharges.

3) Antiepileptic drugs (AEDs) can be a two-edged sword in patients with epilepsy. AEDs increase in synaptic inhibition versus excitation and thereby decrease the risk of another seizure by calming a focus or preventing its generalization but may inhibit optimum working of synapses elsewhere in the brain and lead to more ADHD symptoms. This is especially true with particular AEDs and with polypharmacy. On the other hand, epileptic seizures can impair cognition and executive functions thus prevention of seizures with AEDs can improve attention and behavior problems.

4) ADHD treatments are understudied in patients with epilepsy though available evidence argues for good efficacy and relatively minor risk of worsening seizures for the FDA approved ADHD treatments.

5) ADHD is under-treated in patients with epilepsy and may contribute to suboptimal psychosocial outcomes even when seizures are controlled. The effectiveness of multimodal treatment of ADHD comorbid with epilepsy in improving quality of life outcomes should be studied.

### **8.3 ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN CHILDREN AND ADOLESCENTS WITH OBSESSIVE COMPULSIVE DISORDER (OCD): FACT OR ARTIFACT?**

Daniel Geller, Massachusetts General Hospital

**Abstract:** The extant literature suggests that as many as 30% of children and adolescents with Obsessive Compulsive Disorder (OCD) also satisfy diagnostic criteria for Attention Deficit Hyperactivity Disorder (ADHD). However, ADHD symptoms such as inattention occurring in children with OCD may be an artifact of intrusive obsessional thoughts or anxiety and not true ADHD at all. Whether OCD children with concomitant ADHD-like features have true ADHD or not has important implications. From the clinical standpoint, pharmacological treatment for each disorder diverges so that accurate identification of each syndrome could lead to a more successful treatment approach. From a scientific viewpoint, comorbid ADHD may provide a marker of heterogeneity in OCD useful for clarifying the course, outcome and etiology of the disorder.

We examine the comorbidity of ADHD and OCD using clinical correlates, phenotypic features and family genetic patterns to clarify the association using several large cohorts of children with ADHD, with and without OCD, and children with OCD, with and without ADHD, from consecutively referred pediatric psychiatry patients.

Phenotypic evaluation included all subjects (N=121) meeting full DSM-IV criteria for a diagnosis of ADHD, with (N=67) or without (N=54) OCD and for whom all clinical and structured diagnostic information had been obtained. The number, frequency and types of core ADHD symptoms as well as ADHD-associated functional indices were identical in all youth with DSM-IV diagnosed ADHD irrespective of the presence or absence of comorbid OCD. Family genetic evaluation assessed for ADHD and OCD in the 1533 first-degree relatives of three groups of index children: those with ADHD and OCD, those with ADHD but no OCD

and matched controls with neither disorder. The risk for ADHD was similarly elevated in families of ADHD youth with (18.9%) and without OCD (20.1%)( $p=0.91$ ), and both groups had significantly higher rates of ADHD compared with controls (4.6%)( $p\leq.001$ ) consistent with previous research showing a strong familial risk for ADHD. The risk for OCD was significantly elevated only among relatives of youth with ADHD plus comorbid OCD (13.0%) compared with controls (0.5%)( $p\leq.001$ ) and consistent with previous research showing a strong familial risk for OCD. Relatives affected with ADHD had a significantly elevated risk for OCD compared to relatives unaffected by ADHD (7.4% vs. 1.3%)( $p<0.001$ ) suggestive of co-segregation between these disorders. There was no evidence of nonrandom mating between ADHD- and OCD-affected spouses.

These findings suggest that when ADHD-like symptoms are seen in OCD youth they reflect a true comorbid state of OCD plus ADHD and that the ADHD syndrome may be independent of OCD in comorbid youth. Attention to both disorders is needed to assure best clinical outcomes.

## **9. BIPOLAR DISORDER AS IT RELATES TO ADHD**

**Chair:** Janet Wozniak, Mass General Hospital

**Overall Abstract:** This symposium will address practice-changing advances in the research and understanding of pediatric bipolar disorder and ADHD. Dr Wozniak will provide an overview of pediatric bipolar disorder as a valid diagnosis and provide evidence-based findings regarding its co-occurrence with ADHD. She will review data from clinic and research settings. She will provide information on familiarity, course, treatment, response and biomarker studies, which support the validity of the comorbid condition pediatric bipolar disorder and ADHD.

### **Learning Objectives:**

- Pediatric bipolar disorder is a valid diagnosis with predictable course and clinical characteristics.
- Family genetic studies support the co-occurrence of pediatric bipolar disorder and ADHD.
- Pediatric bipolar disorder has a persistent course.
- Treatment outcomes and biomarker research support the validity of the bipolar and ADHD.

### **9.1 PREDICTIVE UTILITY OF THE CBCL BIPOLAR PROFILE**

Joseph Biederman, Massachusetts General Hospital

**Abstract:** Pediatric bipolar (BP) disorder is a prevalent and highly morbid disorder. While structured diagnostic interviews have been developed to aide in the diagnosis of pediatric BP disorder, these tools are lengthy, costly, and not widely available. One possible diagnostic aid is the Child Behavior Checklist (CBCL).

To assess the diagnostic utility of the Child Behavior Checklist (CBCL)-Bipolar (BP) profile to identify children with a diagnosis of BP-I disorder.

Subjects were derived from four independent datasets of children and adolescents with and without attention deficit hyperactivity disorder (ADHD) and BP-I. Subjects were recruited from pediatric and psychiatric clinics and the community. All subjects had structured clinical interviews with raters blinded to subject ascertainment status. We used an empirically-derived profile from the CBCL consisting of an aggregate t-score from the Attention, Anxiety/Depression, and Aggression subscales (CBCL-BP profile) to operationalize the presence or absence of bipolar symptoms. Receiver operating characteristic (ROC) curves were



used to examine the ability of the CBCL-BP profile to identify children with and without a structured interview diagnosis of BP-I disorder.

The sample consisted of 661 subjects (mean age:  $11.7 \pm 3.3$  years, 57% male, and 94% Caucasian). Twenty percent of participants (N=130) met structured interview criteria for a full diagnosis of BP-I disorder. The ROC analysis of the CBCL-BP profile yielded an area under the curve of 0.91. A t-score of  $\geq 195$  on the CBCL-BP profile correctly classified 86% of subjects with BP-I disorder with 80% sensitivity, 87% specificity, 61% positive predictive value, 95% negative predictive value.

The CBCL-BP profile efficiently discriminated pediatric subjects with and without a structured interview diagnosis of BP-I disorder. Findings suggest that the CBCL-BP profile may be an efficient tool to help identify children who are very likely to suffer from BP-I disorder.

## **9.2 COMORBIDITY WITH ADHD AND COURSE IN A SPANISH SAMPLE OF CHILDREN & ADOLESCENTS WITH BIPOLAR DISORDER**

César Soutullo, DR

**Abstract:** Bipolar disorder (BD) often starts in adolescents, and it has gained validity. Despite substantial research in the last 20 years, its diagnosis is difficult and still controversial in children and early adolescents. Moreover, it is frequently comorbid with ADHD, Oppositional-Defiant and Conduct Disorders, and Mood dysregulation. These comorbidities make differential diagnoses difficult, as there is considerable phenomenological overlap. There is still discussion on the prevalence and longitudinal stability of BD in children and adolescents. Longitudinal studies are needed, especially outside the USA. Our objective is to describe clinical characteristics and naturalistic follow-up, course and diagnostic stability in a sample of children and adolescents with BD recruited during 15 years.

We reviewed the medical records of all children and adolescents (n=72) with DSM-IV BD evaluated at the Child & Adolescent Psychiatry Unit, University of Navarra Clinic (Pamplona, Spain) over a 15-year period. We used the K-SADS-PL template interview for clinical data collection. We evaluated stability of diagnosis at follow-up, response to treatment (% with remission, response, partial response or no response) and outcome (using CGI-S) over time.

75% (n=54) of the sample were boys and 25% (n=18) were girls, with a median follow up period of 3.86 years (mean: 4.56 years). Half of the patients had delay from symptom onset to diagnosis of  $>2$  years (median 2.34 years), but only a few months delay since their first Psychiatric evaluation until diagnosis (median 0.25 years). At first diagnosis, 37.5% (n=27) had BD-I, 8.3% (n=6) BD-II and 54.2% (n=39) BD-NOS. At follow-up, 62.5% (n=45) had BD-I, 8.3% (n=6) BD-II, and 23.6% (n=17) BD-NOS, and only 4.2% (n=3) failed to meet criteria for BD. Two of patients completed suicide during the follow-up period. ADHD was comorbid in 43.7% of cases, but only 28.2% received treatment for ADHD (stimulants or atomoxetine). We found no association of ADHD symptoms at baseline with any particular outcome (BD-I, BD-II, BD-NOS or no diagnosis) at follow-up.

The diagnosis of Pediatric BD was stable time in 95.6% of our sample. Patients with baseline BP-I retained the diagnosis, and many patients with baseline BP-NOS had BP-I at follow-up. ADHD was present in 44.7% of the patients, but ADHD symptoms did not influence outcome, but comorbidity was associated with worse treatment response.

### 9.3 FAMILIAL AGGREGATION AND CO-AGGREGATION OF BIPOLAR DISORDER AND ADHD

Kathleen Merikangas, NIH/NIMH

**Abstract:** The aims of this presentation are to: (1) to provide an overview of the associations between mood disorder subtypes with ADHD; (2) to examine patterns of familial aggregation of Attention Deficit Hyperactivity Disorder (ADHD) and its core components in a community based family study of mood spectrum disorders; and (3) to evaluate patterns of co-aggregation of mood disorder subtypes including Major Depressive Disorder (MDD) and bipolar I (BP1) and bipolar II disorder (BPII) with ADHD.

I will present data from our clinically-enriched community sample of 500 probands who were recruited from the greater Washington, DC metropolitan area, and their 1,035 relatives that was based on standard family study methodology through a best-estimate procedure based on direct semi-structured interviews or family history reports. I will also present data from mobile assessments on the stability and variability of the core features of people with a history of ADHD and mood disorders based on electronic diary assessments.

Our findings indicate that there is specificity of familial aggregation of mood disorders and ADHD. However, there was no co-aggregation between mood disorder subtypes and ADHD in first degree relatives suggesting that there was independence of familial transmission of ADHD and mood disorders. Therefore, our data provide evidence for the specificity of familial aggregation of ADHD and mood disorder subtypes, with limited cross aggregation of ADHD and mood disorders in general. Therefore, the associations with mood disorders are likely attributable either to mood disorder as a consequence of ADHD, or another common underlying risk factor. However, even though there is no diagnostic overlap between these conditions, in-time monitoring of core emotional and behavioral correlates of mood and attention indicates that distractibility is a core state indicator of BD and ADHD. Therefore, the overlap between ADHD and Mood disorders could be in part attributable to shared features of the two purportedly distinct disorders. Future research directions of these findings will be described.

Friday, January 18, 2019

Reception and Poster Session I

7:30 p.m. - 9:00 p.m.

Exhibit Hall C

\*Denotes presenting author.

\*\*Denotes a Data Blitz presentation.

## **F1. A MODIFIED-RELEASE DRUG DELIVERY TECHNOLOGY CONTAINING AMPHETAMINE-ION EXCHANGE COMPLEXES**

Barry Herman<sup>1</sup>, Thomas King<sup>\*1</sup>, Judith Kando<sup>1</sup>, Antonio Pardo<sup>1</sup>

<sup>1</sup>Tris Pharma, Inc.

**Background:** The proprietary, immediate and extended drug delivery technology LiquiXR® utilizes an ion-exchange resin that complexes with amphetamine or any other active moiety that can be protonated and is water-soluble. The active ingredient of the drug product forms a complex with an ion exchange polymer of the resin resulting in very fine, micron-sized particles. A portion of these particles is then coated with an aqueous, pH-independent polymer designed to provide sustained release of drug product. The polymer coating applied to the ion-exchange resin particles is of varying thickness, allowing for extended release of active drug product while uncoated particles provide for immediate release of active drug product.

**Methods:** The release characteristics of LiquiXR allow for customized, sustained release of active drug for up to 24 hours post-dose. Mechanistically, drug particles enter the gastrointestinal (GI) tract. As positively-charged ions from GI fluids diffuse across the coating, it displaces drug ions from product and they diffuse through the coating and into the GI fluids for absorption. As the coating is of variable thickness, some drug product takes longer to diffuse and absorb, providing for the delayed drug release characteristics.

**Results:** The LiquiXR™ drug delivery technology has already been successfully utilized in the development of treatment options (liquid suspension and chewable tablet) that offer rapid absorption and sustained plasma levels after once-daily dosing. LiquiXR is utilized in Dyanavel® XR (amphetamine extended-release oral suspension; AMPH EROS), which is indicated for the treatment of attention-deficit hyperactivity disorder. It comprises 2.5 mg/mL amphetamine base and uses LiquiXR technology to provide an immediate release component followed by an extended-release profile.

**Conclusions:** The efficacy of AMPH EROS was established in children ages 6 to 12 years in a Phase 3, placebo-controlled laboratory classroom study. In that study, ADHD symptoms in children on an individually optimized dose of amphetamine (range 10-20 mg/day) were statistically significantly improved compared with symptoms in children treated with placebo. For children treated with AMPH EROS, onset of effect was demonstrated at 1 hour after dosing, and efficacy was observed through 13 hours post-dose. The effect size was comparable to effect sizes demonstrated for other psychostimulants tested in studies using a similar design. The efficacy data reported for AMPH EROS provides an excellent example of the potential utility and clinical application for other active drug products requiring an immediate release and extended release profile.

## F2. SINGLE DOSE PHARMACOKINETICS OF AMPHETAMINE EXTENDED-RELEASE ORAL SUSPENSION (AMPH EROS) IN CHILDREN AGED 4 TO 5 YEARS OLD WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Barry Herman<sup>1</sup>, Andrea Marraffino<sup>2</sup>, Judith Kando<sup>1</sup>, Thomas King\*<sup>3</sup>, Antonio Pardo<sup>3</sup>, Andrew J. Cutler<sup>3</sup>

<sup>1</sup>Tris Pharma, Inc., <sup>2</sup>Florida Clinical Research Center, LLC, <sup>3</sup>Meridien Research

**Background:** The primary objective of this pharmacokinetic (PK) study was to evaluate the concentration/time profile of amphetamine extended-release oral suspension (AMPH EROS, Dyanavel® XR; Tris Pharma, Inc., Monmouth Junction, NJ) in preschool children (ages 4 to 5 years) following a single 2.5 mg/mL dose of study drug as part of an FDA regulatory requirement.

A previous PK study of AMPH EROS was conducted in children ages 6 to 12 years old diagnosed with ADHD, to evaluate the single-dose (10 mg) plasma amphetamine concentration/time profile of orally administered AMPH EROS. Peak plasma concentrations occurred at a median time of 3.9 and 4.5 hours after dosing, respectively. The mean plasma terminal elimination half-life of d-amphetamine was 10.43 ( $\pm$  2.01) hours and the mean plasma terminal half-life for l-amphetamine was 12.14 ( $\pm$  3.15) hours. These results were consistent with PK data reported for AMPH EROS in adults. Subsequently, a relative bioavailability study was conducted in 29 healthy adult subjects. Following a single, 18.8 mg oral dose of AMPH EROS, the median (range) time to peak plasma concentration (t<sub>max</sub>) for d- and l-amphetamine was 4.0 (2-7) hours after dosing and peak concentrations (C<sub>max</sub>) were 102% and 106% for d-amphetamine and l-amphetamine, respectively, when compared with the C<sub>max</sub> of the IR mixed amphetamine salts tablets. The relative bioavailability of AMPH EROS compared with an equal dose of mixed amphetamine salts IR tablets is 106% of d-amphetamine and 111% for l-amphetamine.

The data from the present study are intended to guide appropriate dosing for future safety and efficacy studies with AMPH EROS in the 4-5 year old (preschool) patient population.

**Methods:** This open-label, single-dose, single-period, single-treatment study was designed to evaluate the PK profile of AMPH EROS in male and female subjects with ADHD aged 4 to 5 years with weight  $\geq$ 28 lbs at screening. All subjects provided written informed consent by both parents or legal guardians and verbal assent prior to administration of study procedures.

Demographics included descriptive statistics for age, sex, race, weight, and height. PK parameters for d- and l-amphetamine in plasma (C<sub>max</sub>, t<sub>max</sub>, AUC<sub>0-t</sub>, AUC<sub>0- $\infty$</sub> , and t<sub>1/2</sub>) were calculated and expressed as means, geometric means, and standard deviations.

The primary endpoint was all objective PK measurements at 28 hours post-dose. Safety was monitored continuously and assessed based on occurrence of adverse events, as well as measurements of vital signs and ECG.

**Results:** Five (5) subjects (2 females and 3 males) completed the study. The mean age of enrolled subjects was 4 years old, with a mean (SD) BMI of 16.2 (1.1).

For d-amphetamine, the mean (SD) C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0- $\infty$</sub>  were 20.920 (2.292) ng/mL, 288.327 (48.096) hr\*ng/mL, and 311.847 (46.287) hr\*ng/mL, respectively. The median (range) t<sub>max</sub> was 2.98 (2.97-3.98) hours and the mean (standard deviation) t<sub>1/2</sub> was 6.81 (1.27) hours.

For l-amphetamine, the mean (SD) C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-∞</sub> were 6.550 (0.739) ng/mL, 96.481 (15.702) hr\*ng/mL, and 106.842 (14.369) hr\*ng/mL, respectively. The median (range) t<sub>max</sub> was 3.98 (2.97-4.02) hours and the mean (standard deviation) t<sub>1/2</sub> was 7.56 (1.56) hours. Study drug was well-tolerated by the subjects in this study.

**Conclusions:** The PK parameters for AMPH EROS in children 4-5 years old measured and assessed in this PK study were consistent with those observed in children aged 6 to 12 years and in adults.

### **F3. AKL-T01, A NOVEL, DIGITAL TREATMENT FOR ADHD REDUCES EX-GAUSSIAN TAU AND INDUCES A SHIFT IN RESPONSE CRITERION IN AN OBJECTIVE TEST OF ATTENTION**

Stephen Faraone\*<sup>1</sup>, Scott Kollins<sup>2</sup>, Elena Cañadas<sup>3</sup>, Jeffrey D. Bower<sup>3</sup>, Jeffrey Epstein<sup>4</sup>, Denton DeLoss<sup>3</sup>

<sup>1</sup>SUNY Upstate Medical University, <sup>2</sup>Duke University, <sup>3</sup>Akili Interactive, <sup>4</sup>Cincinnati Children's Hospital Medical Center

**Background:** Individuals with ADHD characteristically show greater reaction time variability (RTV) in a wide range of tasks compared with typically developing populations (Kofler, et al. 2013). One sensitive indicator of ADHD-related RTV is ex-Gaussian tau, which indicates a positive skew in an individual's RT distribution (Henriquez-Henriquez, et al. 2015). This positive skew represents the preponderance of long RTs which are often interpreted as attentional lapses. ADHD is also associated with a deficit in behavioral inhibition (Winstanley, Eagle, & Robbins, 2006) which is reflected by an increased number of commission errors that may indicate a liberal response criterion. Here we examine whether AKL-T01, a digital treatment with a novel videogame-like interface for ADHD can help to improve these areas of impairment. Data were obtained during the Software Treatment for Actively Reducing Severity of ADHD (STARS-ADHD) randomized clinical trial in children with ADHD (NCT02674633).

**Methods:** Children 8-12 years of age participated with parental consent in a double-blinded active-controlled study of AKL-T01 (N = 180, enrolled), compared with an active-control, AKL-T09 (Words, N = 168, enrolled). Words, an educational word game, was matched for engagement, time on task, and expectation of benefit. Participants were assessed at baseline and then began their assigned treatment for ~25 minutes/day 5 days/week over four weeks. After four weeks of treatment they returned to the clinical site for post-treatment assessment. The primary outcome measure was the Attention Performance Index, API, (a composite normed measure of attention and inhibitory control) from the Test of Variables of Attention (T.O.V.A.®), an FDA-approved objective measure of attention and inhibitory control. The T.O.V.A.® consists of multiple test sections meant to assess different aspects of attention and inhibitory control (Half 1: Infrequent Targets; Half 2: Frequent Targets; and Total: Half 1 and Half 2 combined).

**Results:** AKL-T01 (N=169) showed a significantly greater improvement in their API scores compared with Words (N = 160), p = 0.006. Results also indicate that AKL-T01 showed significantly reduced total standardized RT variance across both test sections compared with Words, p = 0.01. To examine this result in more detail we assessed the parameters of the ex-Gaussian distribution (sigma, mu, and tau) and found that tau was significantly reduced in the AKL-T01 group as compared with the Words group, p < 0.01. To further examine shifts in inhibitory control, we calculated the criterion for each participant to respond that a stimulus was present by calculating the response criterion, c, a common metric for the decision criterion location used in signal detection theory. We found a significantly greater shift in criterion

location towards conservative responses for the AKL-T01 group compared with the Words group in the frequent response portion of the T.O.V.A.®,  $p = 0.03$ . No significant difference between groups was found in the infrequent response section of the T.O.V.A.®.

**Conclusions:** The results of the study show significantly greater improvement in attention and inhibitory control as measured by the T.O.V.A.®, as well as significant improvements in RTV and a more conservative decision criterion. These results considered together suggest that AKL-T01 may be an effective treatment for individuals with ADHD.

#### **F4. SLEEP-ASSOCIATED ADVERSE EVENTS DURING METHYLPHENIDATE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN YOUTH: A META-ANALYSIS**

Stephen Faraone\*<sup>1</sup>, Michelle Po<sup>2</sup>, Marina Komolova<sup>2</sup>, Samuele Cortese<sup>3</sup>

<sup>1</sup>SUNY Upstate Medical University, <sup>2</sup>Ironshore Pharmaceuticals & Development, Inc., <sup>3</sup>Center for Innovation in Mental Health, University of Southampton

**Background:** Sleep disturbances are associated with both attention-deficit/hyperactivity disorder (ADHD) and methylphenidate (MPH) treatment. We sought to assess the risk of sleep-related adverse events (AEs) according to the type of sleep problem and the MPH formulation studied, as well as to determine whether sleep-related AE rates are affected by sample and study design features in trials evaluating MPH in youth with ADHD.

**Methods:** A meta-analysis was conducted on blinded placebo-controlled studies investigating MPH in youth (6–18 years inclusive) with ADHD in a naturalistic setting. Studies published in English were collected via online databases and unpublished sources (www.clinicaltrials.gov and FDA website). Eligibility was reviewed by PhD-trained reviewers and data extraction was conducted in duplicate. Sleep-related AEs (either spontaneous or elicited reports), and formulation and study design features were extracted from each study, with discrepancies resolved by discussion or, if needed, by the senior investigator.

**Results:** Thirty-five studies with 3079 drug-exposed and 2606 placebo-treated patients yielding 75 observations of sleep-related AEs were included. Pooled RRs for sleep-related AEs were significantly higher with MPH. Several sample or study design features, including formulation, doses per day, age, sex, proportion of stimulant responders, study year, number of sites, rater type, and use of a rating scale, significantly predicted the RR for sleep-related AEs and drug studied. After correcting for confounders, significant differences were identified among various MPH formulations. Given the wide range of differences in study methods that can affect absolute AE rates in both drug and placebo groups, it is not surprising that their rates were found to be highly correlated ( $r = 0.89$ ;  $p < 0.0001$ ). Indeed, placebo rates of sleep-related AEs closely predicted the RR of sleep-related AEs, with higher placebo AE rates demonstrating a lower RR between treated and untreated groups. This high correlation enables the prediction of the expected RR based solely on the observed placebo AE rate in the studies reviewed.

**Conclusions:** Sleep-related AEs were associated with MPH, and certain study design and sample features significantly influenced RR. Importantly, the absolute placebo rate of sleep-related AE is a key predictive factor of RR, and interpretations of RR should be considered in the context of the absolute placebo rate. By demonstrating that RR and its interpretation are significantly constrained by the placebo sleep-related AE rate, we provide the field with a useful covariate for adjusting RR statistics.

#### **F5. RELATIONSHIPS AMONG SCORE CHANGES ON THE BROWN ATTENTION-DEFICIT DISORDER SCALE IN ADULTS WITH ADHD: POST-HOC ANALYSES**

## OF TWO SHP465 MIXED AMPHETAMINE SALTS EXTENDED-RELEASE CLINICAL TRIALS

Thomas Brown\*<sup>1</sup>, Jie Chen<sup>2</sup>, Brigitte Robertson<sup>2</sup>

<sup>1</sup>Keck School of Medicine of University of Southern California, <sup>2</sup>Shire

**Background:** Chronic executive function (EF) impairment is a characteristic of attention-deficit/hyperactivity disorder (ADHD). The Brown Attention-Deficit Disorder Scale (BADDSS) assesses 5 clusters of conceptually-related ADHD symptoms associated with EF. In 2 studies in adults with ADHD, SHP465 mixed amphetamine salts (MAS) extended-release produced greater BADDSS total and cluster score reductions than placebo (Pbo), indicating greater EF improvement with SHP465 MAS than Pbo. We examine relationships between BADDSS total and various cluster score changes and between BADDSS cluster and item score changes in the aforementioned studies.

**Methods:** Data from 2 studies (1 dose-optimization; 1 fixed-dose) of SHP465 MAS in adults with DSM-IV-TR-defined ADHD were used. The dose-optimization study randomized adults with baseline ADHD-Rating Scale-IV (ADHD-RS-IV) total scores  $\geq 24$  to SHP465 MAS (12.5–75 mg) or Pbo for 7 weeks; the fixed-dose study randomized adults with ADHD-RS-IV total scores  $\geq 32$  to SHP465 MAS (25, 50, or 75 mg) or Pbo for 6 weeks. The BADDSS was a secondary efficacy endpoint in both studies. Post hoc analyses assessed correlations for changes from baseline to end-of-study (EOS; the last non-missing post-baseline assessment) between BADDSS total and cluster (cluster 1: organizing and activating to work; cluster 2: sustaining attention and concentration; cluster 3: sustaining energy and effort; cluster 4: managing affective interference; cluster 5: using working memory and accessing recall) scores and for BADDSS cluster and individual item score changes in the intent-to-treat (ITT) population.

**Results:** The ITT populations included 268 participants (Pbo, n=132; SHP465 MAS, n=136) in the dose-optimization study and 405 participants (Pbo, n=103; all SHP465 MAS, n=302) in the fixed-dose study. Changes from baseline to EOS in BADDSS total score were positively correlated with all cluster score changes in the dose-optimization study (Pearson correlation coefficient range: Pbo, 0.7295 [cluster 4] to 0.8837 [cluster 1]; SHP465 MAS, 0.6692 [cluster 4] to 0.8952 [cluster 3]) and in the fixed-dose study (Pearson correlation coefficient range: Pbo, 0.7273 [cluster 4] to 0.8923 [cluster 2]; SHP465 MAS, 0.8336 [cluster 4] to 0.9341 [cluster 2]). Changes from baseline to EOS in each cluster were positively correlated with individual item score changes in the dose-optimization study (cluster 1: Pbo [0.4319 to 0.7126], SHP465 MAS [0.3745 to 0.7804]; cluster 2: Pbo [0.4632 to 0.6812], SHP465 MAS [0.6049 to 0.7965]; cluster 3: Pbo [0.3241 to 0.6773], SHP465 MAS [0.4691 to 0.6985]; cluster 4: Pbo [0.5207 to 0.6453], SHP465 MAS [0.3571 to 0.6330]; cluster 5: Pbo [0.4933 to 0.6751], SHP465 MAS [0.5806 to 0.7200]) and in the fixed-dose study (cluster 1: Pbo [0.1912 to 0.6932], SHP465 MAS [0.3771 to 0.7992]; cluster 2: Pbo [0.4464 to 0.7029], SHP465 MAS [0.6154 to 0.8053]; cluster 3: Pbo [0.3085 to 0.6661], SHP465 MAS [0.3461 to 0.7487]; cluster 4: Pbo [0.3530 to 0.6635], SHP465 MAS [0.4924 to 0.7104]; cluster 5: Pbo [0.4475 to 0.5932], SHP465 MAS [0.5742 to 0.7282]).

**Conclusions:** These post hoc analyses indicate that changes from baseline to EOS in BADDSS total and cluster scores were highly positively correlated. BADDSS cluster and items score changes were positively correlated, with some more highly correlated than others probably due to the variation in the specific symptoms of ADHD and cluster of symptoms that individual patients may experience as problematic.



## F6. RESPONSE PROFILE OF A NOVEL, HOME-BASED, DIGITAL TREATMENT FOR PEDIATRIC ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Scott Kollins\*<sup>1</sup>, Elena Canadas<sup>2</sup>, Ann Childress<sup>3</sup>, Raun Melmed<sup>4</sup>, Denton DeLoss<sup>2</sup>, Jacqueline Lutz<sup>2</sup>

<sup>1</sup>Duke University, <sup>2</sup>Akili Interactive, <sup>3</sup>Spring Mountain Treatment Center & Montevista Hospital, <sup>4</sup>Melmed Center

**Background:** There is a need for novel, targeted and safe treatment approaches for patients who suffer from ADHD. Cognitive neuroscience can inform the development of these novel treatments by targeting brain systems and processes that are assumed to be deficient in ADHD. AKL-T01 is a digital treatment delivered through a video game interface targeting neural networks involved in cognitive control, using adaptive algorithms that personalize the treatment to each patient. A proof-of-concept study demonstrated improved cognition and good feasibility in pediatric ADHD. Here we describe responder data of the subsequent randomized Software Treatment for Actively Reducing Severity of ADHD (STARS-ADHD) trial of AKL-T01 versus an active control (AKL-T09) in pediatric patients with ADHD.

**Methods:** STARS-ADHD, a double-blind, active-controlled randomized trial involving 20 clinical sites, recruited children 8-12 years of age with a current diagnosis of ADHD and randomized to either AKL-T01 (n= 180) or the active control, AKL-T09 (Words, n = 168). The Words game was designed to be matched for expectancy, engagement, and time on task. Participants were assessed at baseline at their clinical site, and then began their assigned treatment for ~25 minutes/day 5 days/week over four weeks. They then returned to the clinical site for post-treatment assessment. The primary endpoint was a measure from an objective, computerized test of attention and inhibitory control: the Attention Performance Index (API) from the Test of Variables of Attention (T.O.V.A.®). This FDA-approved test suggests an API cutoff of < 0 as indicating performance similar to ADHD samples. Pre-specified chi-square tests were used to compare responders between AKL-T01 and Words. The proportion of responders for the primary endpoint were pre-specified as T.O.V.A API: A) improvement of >1.4 points or B) post-test score of ≥0. Responder analyses were also conducted on secondary outcomes: parent-rated ADHD symptoms (ADHD-RS), responders defined as ADHD-RS improvement from pre- to post-treatment by 30% (post-hoc); clinician rated ADHD symptom improvement (Clinical Global Improvement; CGI), responder defined as CGI-I post-score of A) ≤2 or B) 1; and ADHD related impairment (Impairment Rating Scale; IRS), responder defined as any improvement from pre- to post.

**Results:** AKL-T01 resulted in T.O.V.A API score improvements of >1.4 points in 46.7% of participants and post-treatment scores of ≥0 in 10.6%. Words had significantly fewer responders of both types: 31.9% ( $\chi^2 = 7.60$ ,  $p = 0.006$ ) and 4.4% ( $\chi^2 = 4.54$ ,  $p = 0.03$ ). Response rates for AKL-T01 were higher or equal than Words for the secondary endpoints: ADHD-RS: AKL-T01 = 24.3%, Words = 18.9%; IRS: AKL-T01 = 48%, Words = 37.3%; CGI ≤2 at post: AKL-T01 = 16.6%, Words = 15.9%; CGI of 1 at post: 0.6% for both. Only the IRS responder rate was significantly different between groups ( $\chi^2 = 3.87$ ,  $p = 0.049$ ).

**Conclusions:** AKL-T01 showed improved response in an objective measure of attention and inhibitory control, indicating that the intervention targets known core deficits in ADHD. Importantly, more than 10% of participants moved to within normal limits suggesting no or minimal attention impairments.

Symptom and impairment measures also indicate clinical benefits of AKL-T01. Additional studies are needed to fully understand the impact on symptoms and impairments and the durability of the effects from AKL-T01.

## **F7. POST-HOC ANALYSES OF REMISSION FROM TWO STUDIES OF SHP465 MIXED AMPHETAMINE SALTS EXTENDED-RELEASE IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER**

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**Background:** There is a lack of consensus regarding the appropriate definition of remission in adults with attention-deficit/hyperactivity disorder (ADHD), with definitions being proposed for syndromatic, symptomatic, and functional remission. In a recently published analysis, 95% of adult ADHD controls had total scores <24 on the 18-item Adult ADHD Investigator Symptom Rating Scale (AISRS), suggesting that this cutoff value on the AISRS could be used as an index of symptomatic remission in adults with ADHD. In 2 studies of adults with ADHD, reductions in ADHD-Rating Scale-IV (ADHD-RS-IV) total score were significantly greater with SHP465 mixed amphetamine salts (MAS) extended-release than with placebo in adults with ADHD. Here, we assess rates of remission for SHP465 MAS versus placebo in the aforementioned clinical studies.

**Methods:** Data from 1 dose-optimization study and 1 fixed-dose study of SHP465 MAS in adults with DSM-IV-TR–defined ADHD were used in these analyses. In the 7-week dose-optimization study, adults with baseline ADHD-RS-IV total scores  $\geq 24$  were randomized to SHP465 MAS (12.5–75 mg) or placebo. In the 6-week fixed-dose study, adults with ADHD-RS-IV total scores  $\geq 32$  were randomized to SHP465 MAS (25, 50, or 75 mg) or placebo. The primary efficacy endpoint in both studies was change from baseline in ADHD-RS-IV total score. The current post hoc analyses examine the percentage of participants exhibiting ADHD symptom remission with SHP465 MAS treatment over time and at study endpoint (the average of the last 3 weeks of treatment or the last post-baseline assessment) in the intent-to-treat population. Based on the total score cutoff value of 24 for the AISRS, a conservative definition of remission (total score  $\leq 12$  on the 18-item ADHD-RS-IV) was used in these analyses. Kaplan-Meier analyses assessed between-group differences in time to remission. Additional analyses will examine factors (e.g., age, sex, baseline symptom count, dose) associated with remission in these studies. The studies were not powered for these post hoc assessments; all reported P values are nominal and descriptive.

**Results:** The intent-to-treat populations included 268 participants (placebo: n=132, SHP465 MAS: n=136) in the dose-optimization study and 405 participants (placebo: n=103, SHP465 MAS: n=302) in the fixed-dose study. In the dose-optimization study, the percentages (95% CI) of participants meeting the remission criterion at endpoint were 27.2% (19.7%, 34.7%) with SHP465 MAS and 9.1% (4.2%, 14.0%) with placebo. In the fixed-dose study, the percentages (95% CI) of participants meeting the remission criterion at endpoint were 29.1% (24.0%, 34.3%) combined across all SHP465 MAS doses (25.2% [16.9%, 33.6%] for 25 mg, 30.7% [21.7%, 39.7%] for 50 mg, and 31.6% [22.4%, 40.8%] for 75 mg) and 4.9% (0.7%, 9.0%) with placebo. In both studies, Kaplan-Meier analyses indicated that time to remission favored SHP465 MAS over placebo (all nominal log-rank  $P < 0.0001$ ).

**Conclusions:** In 2 clinical studies of adults with ADHD, SHP465 MAS was associated with remission rates that were more than twice the magnitude of placebo, with approximately 25%

of those treated with SHP465 MAS meeting the remission criterion. Time to remission also nominally favored SHP465 MAS over placebo.

## **F8. EFFICACY AND SAFETY OF DR/ER-MPH, A DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE, IN CHILDREN WITH ADHD: RESULTS FROM A PIVOTAL PHASE 3 CLASSROOM TRIAL**

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**Background:** Evening-dosed HLD200 is a delayed-release and extended-release formulation of methylphenidate (DR/ER-MPH) designed to delay initial drug release by 8–10 hours to provide an onset of treatment effect upon awakening and lasting into the evening. Herein, we present the efficacy and safety of DR/ER-MPH from a pivotal, multicenter, phase 3, placebo (PBO)-controlled laboratory classroom study that enrolled 125 children (6–12 years) with attention-deficit/hyperactivity disorder (ADHD) (NCT02493777).

**Methods:** During a 6-week open-label (OL) phase, once daily DR/ER-MPH was titrated to an optimal dose (20, 40, 60, 80, or 100 mg/d) and dosing time (8 PM  $\pm$  1.5 h) based on improvements on ADHD Rating Scale IV, Before School Functioning Questionnaire, and Conners' Global Index – Parent. Participants were then randomized 1:1 to double-blind (DB) optimized DR/ER-MPH or PBO for 1 week. The primary endpoint was the model-adjusted average of post-dose Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale combined score (SKAMP CS) over a 12-h laboratory classroom day (8 AM to 8 PM). Key/other secondary measures included the Parent Rating of Evening and Morning Behavior-Revised, Morning (PREMB-R AM) and Evening (PREMB-R PM) subscales, and Permanent Product Measure of Performance-Attempted (PERMP-A) and -Correct (PERMP-C). Safety endpoints included treatment-emergent adverse events (TEAEs), with direct questioning for sleep disturbances.

**Results:** After the OL phase, the mean optimized dose was 66.2 mg and the most common prescribed dosing time was 8 PM (64.1% of participants). Efficacy outcomes were analyzed in 117 participants (64 DR/ER-MPH; 53 PBO). After 1 week of DR/ER-MPH treatment, outcomes over a 12-h classroom day were significantly improved versus PBO: SKAMP CS (least squares [LS] mean  $\pm$  standard error [SE]:  $14.8 \pm 1.17$  vs.  $20.7 \pm 1.22$ ;  $P < 0.001$ ), PERMP-A (LS mean  $\pm$  SE:  $125.8 \pm 8.78$  vs.  $92.1 \pm 9.16$ ;  $P = 0.006$ ), and PERMP-C (LS mean  $\pm$  SE:  $121.2 \pm 8.78$  vs.  $89.0 \pm 9.15$ ;  $P = 0.009$ ). DR/ER-MPH also significantly improved functional impairment versus PBO in the early morning (PREMB-R AM [LS mean  $\pm$  SE]:  $0.9 \pm 0.27$  vs.  $2.7 \pm 0.27$ ;  $P < 0.001$ ) and late afternoon/evening (PREMB-R PM [LS mean  $\pm$  SE]:  $6.1 \pm 0.78$  vs.  $9.3 \pm 0.81$ ;  $P = 0.003$ ). No serious TEAEs or TEAEs leading to discontinuation were reported after dose optimization. The most common TEAEs ( $\geq 5\%$  in any group) were any type of insomnia (DR/ER-MPH: 7.7%; PBO: 9.3%; all mild/moderate in severity) and increased diastolic blood pressure (DR/ER-MPH: 13.8%; PBO: 13.0%).

**Conclusions:** Evening-dosed DR/ER-MPH demonstrated significant improvements in ADHD-related symptoms over a 12-h classroom day and functional impairment during the early morning and late afternoon/evening versus PBO in children with ADHD. DR/ER-MPH was well tolerated, with no differences in TEAEs compared to placebo after dose optimization.

## F9. SINGLE-DOSE PHARMACOKINETICS OF KP415, AN INVESTIGATIONAL PRODUCT CONTAINING THE PRODRUG SERDEXMETHYLPHENIDATE (SDX), IN CHILDREN AND ADOLESCENTS WITH ADHD

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<sup>1</sup>KemPharm, Inc., <sup>2</sup>Worldwide Clinical Trials

**Background:** KP415 is an investigational ADHD product designed to provide a rapid onset and extended duration of symptom improvement. To achieve this profile, the drug product contains both serdexmethylphenidate (SDX), a prodrug of d-methylphenidate that is gradually converted to d-MPH over many hours, and d-MPH HCl, which provides rapid exposure to d-MPH following administration. KP415 has been co-formulated as fixed molar dose ratios of 70% SDX:30% d-MPH HCl. The objective of this study was to examine the single-dose pharmacokinetics (PK) of KP415 in children and adolescents with ADHD, and secondarily, to determine the effect of body weight on the PK properties.

**Methods:** This was a single-dose, single-period study of oral administration of KP415 capsules in children (6 to 12 years) and adolescents (13 to 17 years) with ADHD. Following a standardized meal, eligible subjects (N=30) received treatments that were stratified into 3 age and 2 dose groups, whereby 6 to 8 year-olds (Cohort 1, n=10) received 28/6 mg, 9 to 12 year-olds (Cohort 2, n=10) received 56/12 mg, and 13 to 17 year-olds (Cohort 3, total n=10) received either 28/6 mg (n=5) or 56/12 mg (n=5). The combined dose of SDX and d-MPH HCl in each capsule contained the same molar d-MPH as 20 and 40 mg d-MPH HCl, respectively. Blood samples for PK were collected pre-dose and at 0.5, 1, 2, 4, 8, 10, 12, 13, 24, 36, and 48 hours post-dose. Adverse events were continuously recorded, and safety assessments were conducted throughout the study.

**Results:** Mean ages and weights were 7.0 years and 29.3 kg in Cohort 1, 10.1 years and 39.8 kg in Cohort 2, and 13.9 years and 65.4 kg in Cohort 3. Dose-normalized (to the 56/12 mg dose) peak and overall exposure to d-MPH was highest in Cohort 1 ( $C_{max} = 34.4$  ng/mL,  $AUC_{0-24} = 362.0$  h\*ng/mL), followed by Cohort 2 ( $C_{max} = 25.9$  ng/mL,  $AUC_{0-24} = 294.1$  h\*ng/mL), and lowest in Cohort 3 ( $C_{max} = 17.8$  ng/mL and 14.0 ng/mL, for the low and high doses, respectively;  $AUC_{0-24} = 195.0$  ng/mL and 171.1 h\*ng/mL, respectively). When scaled by body weight, mean dose-normalized  $C_{max}$  (range across the 3 cohorts: 25.0 – 25.3 ng/mL/(mg/kg)) and  $AUC_{0-24}$  (range across cohorts: 259.4 – 291.8 (h\*ng/mL)/(mg/kg)) values were similar across cohorts. Median time to peak d-MPH exposure ( $T_{max}$ ) was 4 hours in all cohorts. Clearance (CL/F) values were lower in Cohorts 1 and 2 (96.85 and 97.44 L/h, respectively) than Cohort 3 (170.3 L/h for low dose and 172.3 L/h for high dose), although when adjusted for weight differences, clearance values were similar. A nonlinear regression model evaluating allometric scaling indicated a moderate correlation ( $R^2=0.628$ ) between d-MPH clearance (CL/F) and body weight and a weak correlation ( $R^2=0.200$ ) between d-MPH volume of distribution (VZ/F) and body weight. The geometric means and 95% CIs were within the target range of 60% to 140% for d-MPH CL/F for all cohorts, and for VZ/F in all but one cohort. A total of 5 subjects reported AEs, none of which were serious or led to discontinuation.

**Conclusions:** Dose-normalized systemic exposure to d-MPH following oral administration of KP415 was higher in younger children, which appears to be due to lower clearance in younger children which is, in turn, primarily related to intrinsic body weight differences across the age spectrum examined in this study. These findings are consistent with prior studies of methylphenidate products and indicate that KP415 produces predictable, age-dependent exposure to d-MPH in pediatric subjects.

## **F10. DOSE-PROPORTIONALITY AND STEADY-STATE PHARMACOKINETICS OF KP415, AN INVESTIGATIONAL ADHD PRODUCT CONTAINING SERDEXMETHYLPHENIDATE (SDX), A NOVEL PRODRUG OF D-METHYLPHENIDATE**

Rene Braeckman\*<sup>1</sup>, Sven Guenther<sup>1</sup>, Travis Mickle<sup>1</sup>, Andrew Barrett<sup>1</sup>, Adam Smith<sup>1</sup>, Wei Zhang<sup>2</sup>, Kathryn Roupe<sup>2</sup>, Cynthia Zamora<sup>2</sup>

<sup>1</sup>KemPharm, Inc., <sup>2</sup>Worldwide Clinical Trials

**Background:** KP415 is an investigational ADHD product containing serdexmethylphenidate (SDX), a novel prodrug of d-methylphenidate (d-MPH), co-formulated with d-MPH HCl in fixed molar dose ratios of 70% SDX:30% d-MPH HCl. KP415 has been designed as a once-daily, oral product that provides both early exposure to d-MPH and sustained exposure throughout the day. This study assessed the pharmacokinetics (PK) and dose-proportionality of single KP415 doses, as well the steady-state PK after multiple-dose administration of the highest clinical daily dose.

**Methods:** This was a Phase 1, open-label, randomized, single-dose, 3-treatment, 3-period crossover study evaluating KP415 doses of 28/6 mg, 42/9 mg, and 56/12 mg. These treatments contain combined total doses that are equimolar to 20 mg, 30 mg, and 40 mg d-MPH HCl. Following the single-dose phase, all subjects received 4 doses of 56/12 mg/day KP415 q24h for evaluating the steady-state PK. All doses were administered orally under fasted conditions in healthy adults (n = 23). Plasma samples were collected from pre-dose through 72 h post-dose in the single-dose phase, and in the multiple-dose phase from pre-dose through 24 h post-dose on Days 1-3 (with sparse sampling on Days 2-3), and from pre-dose to 72 hours on Day 4. Safety assessments were performed throughout the study.

**Results:** After single-dose KP415 administration, d-MPH plasma concentrations increased rapidly for all dosage strengths, with peak concentrations (C<sub>max</sub>) of 7.15, 9.88, and 13.85 ng/mL for the 28/6 mg, 42/9 mg, and 56/12 mg doses, respectively. Plasma d-MPH concentrations decreased gradually after C<sub>max</sub>, with appreciable concentrations still apparent at 13 h post-dose. Analyses using a pre-specified power analysis indicated that KP415 was dose-proportional with respect to d-MPH exposure across the tested 2-fold dose-range and predicted to be proportional across a 6.5-, 11.1-, and 82.7-fold range of doses for C<sub>max</sub>, AUC<sub>last</sub>, and AUC<sub>inf</sub>, respectively. In the multiple-dose phase, mean maximum (C<sub>max</sub>), minimum (C<sub>min</sub>), and overall (AUC<sub>0-24h</sub>) d-MPH exposure were approximately 35%, 12%, and 36% higher, respectively, after multiple doses (Dose 4) of KP415, 56/12 mg, relative to a single dose (Dose 1), as expressed by least square geometric means of parameters values. Steady-state plasma concentrations, as assessed by trough concentrations of d-MPH, were achieved prior to the third dose (i.e., between the second and the third day of multiple dosing). Intact prodrug did not accumulate during q24 h dosing. The most frequently reported adverse events (AEs) were dizziness, tachycardia, and feeling jittery, each reported by 3 (12.5%) subjects. There were no serious AEs.

**Conclusions:** KP415 produced dose-proportional increases in the rate and extent of d-MPH exposure across a relatively wide range of doses, with steady-state plasma concentrations achieved prior to the third dose. KP415 has the potential to provide a rapid onset and extended duration of therapeutic benefit, with predictable d-MPH exposure during titration and maintenance.

## **F11. A NOVEL TEXT MESSAGE INTERVENTION TO IMPROVE ADHERENCE TO STIMULANTS IN ADULTS WITH ADHD**

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**Background:** ADHD is a prevalent neurobiological disorder that has been associated with a wide range of adverse outcomes. Data from large datasets document that stimulants decrease the risks for many adverse outcomes, yet compliance with stimulants remains very poor. The main aim of this study was to assess the effectiveness of a novel text messaging intervention aimed at improving the poor rate of adherence to stimulant medications in adults with ADHD. We hypothesized that an ADHD-centric text messaging intervention would improve adherence to stimulant treatment in adults with ADHD.

**Methods:** Subjects were adults with a DSM V diagnosis of ADHD, 18-55 years of age, consecutively referred to the Adult ADHD Program at the Massachusetts General Hospital (MGH) who consented to receive two text messages daily. For comparison purposes, we identified adult patients from the Partners HealthCare electronic medical records (EMR) who had been prescribed stimulant medications between January 1, 2015 and December 31, 2016 using the Partners HealthCare Research Patient Data Registry (RPDR). We matched these patients to our text messaging intervention subjects at a 10-to-1 ratio based on age and sex. We defined a patient in the SMS group as being engaged in treatment (patient engagement) if they refilled their stimulant prescription after the onset of the text messages. We determined whether patients had timely prescription refills using prescriptions documented in their electronic medical record (EMR). For the RPDR comparators, we defined a patient as being engaged a priori if the index stimulant prescription was refilled in a timely fashion.

**Results:** Our results showed that 43% of patients receiving treatment as usual refilled their prescriptions in a timely fashion promptly enough to be considered consistently medicated. In contrast 91% of the SMS intervention group refilled their prescriptions in a timely manner.

**Conclusions:** These data indicate that a novel ADHD centric digital health intervention using text messaging significantly improves patient engagement to treatment with stimulants in adults with ADHD. These findings provide strong support for the utility of this readily accessible, inexpensive and widely available technology to improve the poor rate of adherence to stimulant treatment in adults with ADHD. Cell phones are widely adopted by men and women of all ages, races, incomes, education levels, and geographic locations. More efforts are needed to replicate these findings and extend them to other age groups and clinical settings. To the best of our knowledge, this study is the first digital health technology-based intervention aimed at improving adherence to stimulant medication for adults with ADHD.

## **F12. TRAJECTORIES OF CLINICAL CHANGE MECHANISMS IN A COGNITIVE BEHAVIORAL INTERVENTION FOR COLLEGE STUDENTS WITH ADHD**

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**Background:** The evidence for the efficacy of cognitive-behavioral treatment (CBT) for adults with ADHD continues to grow (Knouse et al., 2017). Although most CBT trials examine effects pre and post treatment, few assess clinical change during treatment. Hence, it is unknown whether trajectories of clinical change mechanisms follow a linear pattern (steadily increasing over time) or a non-linear pattern (reflecting an inconsistent change rate). Although one might expect improvement to be steady and linear in psychosocial interventions, this is often not the case (Hayes et al., 2007). The aim of the current study is to examine trajectories of change over

time in three theorized clinical change mechanisms of ACCESS, a cognitive-behavioral treatment for college students with ADHD. Currently, ACCESS is being tested in an IES-funded multi-site efficacy trial. Preliminary analyses show reductions in ADHD symptoms and improvements in functioning. The current study will examine the trajectories of knowledge of ADHD, behavioral strategy use, and adaptive thinking strategy use during the first eight sessions of ACCESS.

**Methods:** Participants were 119 college students with ADHD (M age = 19.58; SD = 2.81). The sample was 66.40% female and 66.39% Caucasian. Weekly surveys assessing knowledge (two items), behavioral strategies (five items), and adaptive thinking (five items) were administered via email. Participants had 72 hours to complete the survey.

**Results:** Growth curve modeling was used to examine trajectories of knowledge, behavioral strategies and adaptive thinking during treatment. A random intercept-only model was examined first, and if indicated, a linear growth term was added to the model. Quadratic and cubic model terms were added when indicated (Bollen & Curran, 2006). Analyses were conducted in SPSS 25.

In the final model for knowledge, there was a significant positive linear effect ( $\beta = .13$ , SE = .02,  $p < .001$ ), suggesting a steady rate of increase in knowledge over time. In the final model for behavioral strategies, significant effects included a positive linear effect ( $\beta = 5.66$ , SE = 1.12,  $p < .001$ ), a negative quadratic effect ( $\beta = -1.06$ , SE = .24,  $p < .001$ ), and a positive cubic effect ( $\beta = .07$ , SE = .02,  $p < .001$ ). This suggests an “S” curve in behavioral strategy use over time. In the final model for adaptive thinking, significant effects included a positive linear effect ( $\beta = .85$ , SE = .22,  $p < .001$ ) and a negative quadratic effect ( $\beta = -0.49$ , SE = .02,  $p < .05$ ). This indicates adaptive thinking increased, but the rate of change was not consistent.

**Conclusions:** Knowledge of ADHD increased steadily in a linear trend, but trajectories of behavioral strategy use and adaptive thinking use were non-linear. It appears emerging adults with ADHD attending college do not show a steady increase in skill use through treatment. Behavioral strategy use showed a cubic trend, which is best represented by an S-shaped curvilinear pattern. This suggests an initial increase in behavioral strategy use, followed by a flattening or decrease before another rise. Adaptive thinking use demonstrated a quadratic pattern. Use of this skill rose slowly at first before rising more rapidly over time. These results could reflect difficulties in implementing strategies, which is a notable concern in CBT for adults with ADHD (see Ramsay & Rostain, 2016). Finally, knowledge showed a linear pattern, suggesting a steady positive increase. This may indicate increasing knowledge of ADHD does not require implementation outside of session, in contrast to use of strategies.

### **F13. Treatment-Emergent Affective Adverse Effects of Three Stimulant Preparations**

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**Background:** Stimulant treatment often ameliorates the high negative emotionality that frequently accompanies ADHD, but it can also exacerbate it. Data from a clinical trial for highly aggressive children with ADHD that included an open stimulant optimization phase, offered the opportunity to examine alterations in affective symptoms that accompanied changes in specific medication and dose.

**Methods:** Trial participants were boys and girls aged 6 to 12 years inclusive. Eligibility criteria included ADHD, ODD/CD, prior treatment with a stimulant ( $\geq 30$  mg methylphenidate/d or equivalent), and surpassing thresholds on standardized behavior rating scales. Exclusion



criteria included major depression, bipolar disorder, intellectual developmental disorder, and autistic disorder.

Treatment began with a protocol to establish optimal stimulant dosage and concurrent family-based behavioral therapy. Three medications, all long-acting products, were utilized: OROS methylphenidate (a triphasic release preparation [MPH-TRI]), a beaded methylphenidate preparation for biphasic release (MPH\_BI), and mixed amphetamine salts (MAS-XR). All other medications children were taking at study entry were discontinued. Medication dose changes, and switches in medication class as needed, were undertaken at weekly office visits. Measured outcomes included parent-completed rating scales, the Conners' Global Index (ConnGI-P), Retrospective-Modified Overt Aggression Scale (R-MOAS), and the Barkley Behavior and Adverse Effects Questionnaire (BBAEQ). The Child Behavior Checklist was completed at baseline and at the end of stimulant optimization.

**Results:** Participants' stimulant treatment just prior to study entry included MAS-XR (n=27), MPH-TRI (n=50), long-acting dexamethylphenidate (D-MPH-XR; n=22), lisdexamfetamine (LY-AMP; n=40), and other preparations (n=16). Patients treated with LY-AMPH at baseline who then were switched to other stimulant preparations during the study's lead-in protocol showed the highest baseline severity and the largest improvement on two measures: aggressive behavior (Baseline Medication x Time [adjusting for dose],  $F(3, 112)=4.38$ ,  $p = .01$ ) and emotional lability  $F(3, 112)=4.83$ ,  $p = .01$ ). Change in internalizing symptoms was also the largest for those discontinuing LY-AMPH, but the interaction was not significant. There was no effect of pre-enrollment stimulant treatment on baseline magnitude nor change of ADHD symptoms.

**Conclusions:** Findings suggest that among children with ADHD and aggressive behavior, some stimulant preparations may contribute to higher levels of affective symptomatology and behavioral volatility, which resolve after switching to other compounds. These observational data warrant further study to account more effectively for potential confounds. Examination of individual child factors that might heighten susceptibility to treatment-emergent affective adverse outcomes would also contribute both to treatment planning and to understanding how these medications influence affective symptoms.

#### **F14. SUBTLE MOTOR SIGNS AS A BIOMARKER FOR EFFECTIVE MINDFUL MOVEMENT INTERVENTION IN CHILDREN WITH ADHD**

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**Background:** Movement-based mindfulness practices, predominantly adapted from south- and east-Asian societies, have garnered increasing recognition in recent years among western medical communities. Benefits for improved behavioral and emotional regulation, broadly reported in testimonials from practitioners, have been recently supported in a number of studies. Relatedly, our group and others have posited that a movement-based orientation may be highly useful in understanding the bases of Attention Deficit Hyperactivity Disorder (ADHD). Preliminary evidence supports the potential benefit of mindful movement interventions like Tai Chi or Yoga for ADHD. However, these studies, which were principally with adults, have focused on changes in subjective ratings of ADHD-associated behaviors. More rigorous trials require a biomarker that can be administered in a reliable and blinded fashion. We therefore implemented a movement-based mindfulness practice (Tai Chi) for

children with ADHD, hypothesizing that an ADHD-relevant measure of motor control could serve as predictive biomarker of improvement in ADHD symptoms.

**Methods:** Children with ADHD aged 8.2 to 12.8 years of age were recruited for an 8-week Tai Chi intervention. Parent-completed questionnaires were collected to index improvement of ADHD symptoms in conjunction with four candidate motor system biomarkers that demonstrate population correlation with ADHD symptoms, including the Physical and Neurological Examination for Subtle Signs (PANESS). Motor measures were examined for significant improvement following Tai Chi training, as well as for significant correlation with improvements in parent-reported ADHD symptoms.

**Results:** Parent surveys indicated a broad and significant reduction in ADHD symptoms following Tai Chi training ( $p < .02$  for all subscales). Of the four candidate motor measures with sufficient data, we found significant improvement on the PANESS ( $p < .002$ , with a Bonferroni corrected threshold of .013). Critically, improvements in PANESS were significantly correlated with the improvements in ADHD symptoms.

**Conclusions:** Our results provide further evidence for a beneficial effect of mindful movement training for children with ADHD, observing these effects in a younger cohort than previously reported. We extend previous findings by proposing the PANESS as a candidate motor biomarker for future trials of mindful movement interventions.

## **F15. PERCEIVED STIGMA AND THE POSITIVE ILLUSORY BIAS IN CHILDREN WITH ADHD**

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**Background:** Despite displaying significant impairments across a variety of domains, children with ADHD have been found to over-estimate their academic, social, and behavioral competence. This phenomenon of having overly positive self-perceptions of competence in comparison to external measures of competence has been termed positive illusory bias (PIB). The self-protection theory of PIB suggests that PIB is a defensive response to the negative feedback children with ADHD frequently receive, and an attempt to protect against feelings of inadequacy and low self-esteem. The present study aims 1) to test the self-protection theory of PIB in children with ADHD by examining the relationship between perceived stigma and PIB in the social and academic domains, and 2) to examine if age, gender, race/ethnicity, ADHD symptomology, and comorbid symptomology are related to PIB.

**Methods:** Data were collected from 100 children with and without ADHD and their mothers through an online survey. Surveys measured ADHD symptoms, self-perceived competence in social and academic domains, external reports of competence in social and academic domains, perceived stigma, and comorbid symptoms of depression, aggression, and anxiety. Social and academic PIB were measured continuously, and calculated by creating standardized discrepancy scores between child-reported competence and external reports of competence in both social and academic domains.

**Results:** Linear regression analyses were conducted with perceived stigma predicting PIB scores in social and academic domains. Linear regression was also used to examine how PIB scores are associated with gender, age, racial/ethnic background, ADHD symptomology (inattentive and hyperactive/ impulsive symptoms), and comorbid symptomology (depressive, aggressive, and anxious symptoms). Intriguing results as to the relationship between perceptions of stigma and PIB, and the relationship between participant characteristics and PIB emerged.

**Conclusions:** Previous studies suggest that PIB is maladaptive for children with ADHD, as it is associated with a variety of negative outcomes, including poor response to treatment. This indicates that it may be important to assess and address PIB as part of treatment for ADHD, however it has remained unclear how PIB should be addressed. Findings of the present study increase our understanding of the function of PIB in children with ADHD, and which children are most likely to display this bias. Thus, findings have important implications for how PIB might best be addressed in order to reduce the likelihood of negative outcomes for children with ADHD.

## **F16. MEDICATION ACCEPTANCE AMONG AFRICAN AMERICAN PARENTS OF CHILDREN WITH ADHD**

Amy Glasofer\*<sup>1</sup>

<sup>1</sup>Virtua

**Background:** Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral pediatric disorder in the United States. The symptoms of ADHD convey significant morbidity for both the child and family. Medications are a recommended component of treatment for ADHD as they are effective in treating the core symptoms and have a protective effect from related morbidity and mortality; however, only about 62% of children with ADHD receive medications. Moreover, children of ethnic minorities with ADHD are two to five times less likely to receive pharmacotherapy than their White counterparts. Low socio-economic status (SES) acts as an additional barrier. Therefore, these disparities need to be addressed to ensure that all children with ADHD receive comprehensive treatment to succeed through their adolescence. Therefore, the purpose of this grounded theory study is to generate a theory explicating the process of medication acceptance among low-income African American caregivers of children with ADHD.

**Methods:** The design for this study is grounded theory, following a constructivist approach explicated by Charmaz. The sample for this study will be drawn from a pediatric behavioral health center and a city-wide health information exchange in the city of Camden, New Jersey. The inclusion criteria are English speaking parents or legal guardians who identify as African American of Medicaid or uninsured school-aged children, age 5-17, who have been prescribed a medication for management of ADHD within the past year, with or without comorbid behavioral diagnoses. It is anticipated that 15-20 participants will be interviewed to meet the requirements for theoretical sampling. Subsequent procedures for this study will follow methods for constructivist grounded theory described by Charmaz, involving the following in an iterative process: data collection and initial coding; initial memos and focused coding to arrive at conceptual categories; theoretical sampling to seek specific data; advanced memos to refine conceptual categories; memo writing, sorting and further refining categories to arrive at theoretical concepts; identification of core concept and diagramming of concepts; generation of theory; and writing of the draft.

**Results:** This study remains in progress and no results are available at this time.

**Conclusions:** Successful completion of this study would provide the foundation for clinicians to deliver evidence-informed culturally-sensitive interventions to improve medication acceptance among low-income African American caregivers of children with ADHD.

## **F17. FACTORS ASSOCIATED WITH ADHD MEDICATION USE IN COMMUNITY CARE SETTINGS**

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**Background:** Stimulants are a first-line treatment for school-aged children with attention-deficit/hyperactivity disorder (ADHD), yet there is considerable variation in which children are prescribed stimulants. We hypothesized that the likelihood of ADHD medication receipt would be lower in groups with specific patient socio-demographic (e.g., female gender, non-white race) and clinical (e.g., comorbid conditions) characteristics as well as physician characteristics (e.g., older age, more years since completing training).

**Methods:** A retrospective cohort study was conducted with 577 children (mean age = 7.8 years, 70% male) presenting for ADHD to 50 community-based practices. The bivariate relationship between each patient- and physician-level predictor and whether the child was prescribed ADHD medication was assessed. A multivariable model predicting ADHD medication prescription was conducted using predictors with significant ( $p < .05$ ) bivariate associations.

**Results:** 69% of children were prescribed ADHD medication in the year following initial presentation for ADHD-related concerns. Eleven of thirty-one predictors demonstrated a significant ( $p < .05$ ) bivariate relationship with medication prescription. In the multivariable model, being male (OR = 1.34, 95%CI: 1.01-1.78,  $p = .02$ ), living in a neighborhood with higher medical expenditures (OR = 1.11 for every \$100 increase, 95%CI: 1.03-1.21,  $p = .005$ ), and higher scores on parent-inattention ratings (OR = 1.06, 95%CI: 1.03-1.10,  $p < .0001$ ) increased the likelihood of ADHD medication prescription.

**Conclusions:** We found that some children, based on socio-demographic and clinical characteristics, are less likely to receive an ADHD medication prescription. An important next step will be to examine the source and reasons for these disparities in an effort to develop strategies for minimizing barriers to receipt of evidence-based treatment.

## F18. ADHD COACHING MODES OF DELIVERY: FREQUENCY AND EFFICACY

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**Background:** A literature review of research on outcomes of ADHD coaching (Ahmann, Saviet & Tuttle, 2017; Ahmann, Tuttle, Saviet & Wright, 2018) demonstrated effectiveness of coaching for individuals with ADHD but did not report data on delivery mode (in-person, telephone, video-conference). No study of coaching for this population to date has either explored the frequency of use of different coaching delivery modes or compared coaching efficacy by mode, leaving important questions as yet unanswered in the literature.

**Methods:** This mixed methods exploratory study had two components. First, the extant literature on ADHD coaching was examined to identify delivery modes used. Second, a survey exploring delivery mode use was conducted in a convenience sample of ADHD coaches. All social media platforms of the ADHD Coaches Organization (ACO) were employed to invite coaches to participate in the online survey. The survey investigated: frequency of, reasons for, as well as both benefits and concerns related to various modes of ADHD coaching delivery. Categorical questions and Likert scales were used to collect quantitative data, and open-response questions were used to collect qualitative data. SPSS statistical software was for quantitative data analysis. Qualitative data was analyzed using an inductive approach based in

Grounded Theory, a widely used analytic approach that employs an emergent analysis strategy to examine the patterns and themes identify in the data.

**Results:** Data describing coach respondents is reported, including coach certification and/or degree and number of years coaching. Also, the relative frequency of use for each coaching delivery mode, factors determining choice of mode, and coaches' perceived effectiveness of each mode are detailed. Finally, coaches' perceptions of both the benefits and drawbacks of each coaching mode are described.

**Conclusions:** This study exploring modes of ADHD coaching delivery is the first to examine the important questions of (1) frequency of use of each different modes and (2) each mode's efficacy. The relative frequency of use of in-person, telephone, and video-conference delivery modes provides direct insight into process of ADHD coaching. Further, the data on coaches' perceived efficacy of each delivery mode provides a preliminary understanding of efficacy that should be further explored in future research using experimental designs.

**References:**

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## **F19. SLUGGISH COGNITIVE TEMPO (SCT) PREVALENCE RATES IN AN ADHD-REFERRED OUTPATIENT SAMPLE: IMPACT OF REPORTING SOURCE AND FUNCTIONAL IMPAIRMENT CRITERION**

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**Background:** Sluggish cognitive tempo (SCT) refers to excessive levels of daydreaming, mental confusion and sluggish-lethargic behavior. Despite similarities with characteristics of attention-deficit/hyperactivity disorder (ADHD), SCT has been proposed to be a separate diagnosis. Prevalence of SCT as a diagnostic entity in the general population is estimated to be 5.1%. However, rates of SCT in adult psychiatric outpatients have not been examined, particularly whether SCT occurs more frequently among adults diagnosed with ADHD. Further, studies are needed to examine how rates of SCT vary as a function of reporting source and inclusion of functional impairment criterion in adult outpatients. The overall aim of this study was to examine the prevalence of SCT in an ADHD-referred outpatient sample using self and collateral reporting sources.

**Methods:** Adult outpatients seeking an evaluation for ADHD (N = 124) completed a standardized measure of SCT symptoms and functional impairment associated with SCT symptoms. Collateral reports were available for 120 of the 124 cases. SCT symptom thresholds from age-based norms corresponding to the 92nd or 93rd percentile (depending on patient age) were used. Chi-square analyses were conducted to examine the rate of SCT in ADHD (n = 80) and non-ADHD clinical controls (n = 44) as a function of: (a) reporting source (i.e., symptom endorsements based on self report only, collateral report only, either reporting source [an “or” rule], or both reporting sources [an “and” rule]) and (b) the inclusion of a functional impairment criterion (i.e., impairment in  $\geq 1$  domain and impairment in  $\geq 2$  domains).

**Results:** Rates of SCT ranged from 35% to 82% of the total sample depending on reporting source and inclusion of a functional impairment criterion. When rates of SCT were examined

based on ADHD status, 40%-91% in the ADHD group and 27%-66% in the control group met SCT criteria using different reporting sources and impairment criterion. Rates of SCT were higher in the ADHD group than the control group when SCT was based on collateral reporters ( $p$ 's ranging from .009 to .025) or adopting an "or" rule for symptom endorsement across reporting sources ( $p$ 's ranging from <.001 to .004), regardless if a functional impairment criterion was imposed. The higher rates of SCT in the ADHD sample compared to controls approached significance based on self report when symptom count only was used to diagnosis SCT or when symptom count plus impairment in two or more settings was imposed; however, rates of SCT did not differ between groups when an "and" rule for symptom endorsement was adopted, regardless if a functional impairment criterion was used.

**Conclusions:** SCT is more common in adults with ADHD in comparison to non-ADHD adults when SCT is based on collateral reporting sources. However, SCT is endorsed in at least a quarter of adult outpatients without ADHD when symptom count and impairment criteria are imposed, indicating that SCT emerges separate from ADHD in clinical outpatient settings.

## **F20. EVENINGNESS DIURNAL PREFERENCE: PUTTING THE "SLUGGISH" IN SLUGGISH COGNITIVE TEMPO AMONG ADULT OUTPATIENTS?**

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**Background:** Sluggish cognitive tempo (SCT) has been shown to be a key clinical construct that is separate from ADHD but associated with a range of clinical and functional outcomes. Our recent work has shown that SCT symptoms can be reliably assessed among adult outpatients using the SCT subscale of the Barkley Adult ADHD Rating Scale-IV (BAARS-IV) and encompass three factors: daydreamy, sluggish, and low initiation/persistence. There is growing interest in the role of sleep/circadian functioning in SCT presentations, and several aspects of sleep, such as sleep quality, sleep disturbances, and daytime sleepiness, are related to SCT in adult samples. Less is known about circadian/diurnal preference and SCT, which is a critical gap in the literature given the high rates of eveningness preference in adult ADHD samples. A prior population study suggested that eveningness was associated with greater SCT among adults; however, this topic has yet to be investigated in a clinical sample. This study is the first to investigate a relationship between diurnal preference and SCT among adult outpatients, as well as the first to examine associations between diurnal preference and the three SCT factors.

**Methods:** Fifty-two adults (age  $M = 40$ ,  $SD = 13$ ; 60% male) seeking an evaluation for ADHD were recruited from an outpatient psychiatry clinic at a university medical center. Participants completed the 13 item Composite Morningness Scale (CMS), and participants and a collateral reporter (e.g., spouse, parent, or friend) each completed a 9-item SCT scale (BAARS-IV; self- and other-reports) and the Conners' Adult ADHD Rating Scale - Long Form (CAARS; self- and observer-reports). Covarying for age, sex, and ADHD symptom severity, we used linear regression to assess the relationships between diurnal preference on the CMS and a) total SCT symptoms and b) each SCT factor. Analyses were completed separately for self- and other-report of SCT.

**Results:** Greater eveningness was associated with greater total SCT symptom severity when assessed via self-report ( $F(4, 41) = 4.78$ ,  $p = .04$ ), but not by other-report ( $F(4, 42) = 2.37$ ,  $p = .13$ ), after covarying for age, sex, and ADHD symptom severity. Regarding SCT factors, greater eveningness was correlated with greater endorsement of the sluggish factor by both self- ( $F(4, 42) = 11.73$ ,  $p = .001$ ) and other-report ( $F(4, 42) = 6.50$ ,  $p = .01$ ) after controlling

for age, sex, and ADHD symptom severity. Diurnal preference was not associated with the daydreamy or low initiation/persistence factors by either reporter.

**Conclusions:** Greater eveningness preference is associated with greater overall self-reported SCT, and this association appears to be driven primarily by a relationship between diurnal preference and the sluggish SCT factor, which was consistently found across reporters. In addition, these associations are robust after controlling for ADHD symptom severity, age, and sex. Findings suggest a potential role of eveningness diurnal preference in the presentation of SCT, and future studies should investigate the underlying mechanisms linking these two constructs as well as the efficacy of circadian treatments, such as melatonin and light therapy, in the treatment of SCT among adult outpatients.

## **F21. COLLATERAL RATINGS OF CHILDHOOD SYMPTOMS AMONG ADULT OUTPATIENTS SEEKING AN EVALUATION FOR ADHD**

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**Background:** Retrospective questionnaires are an important mechanism for ascertaining onset and severity of childhood symptoms for adults seeking an ADHD evaluation. Despite limitations of retrospective recall, these questionnaires are often the only source of information for assessing childhood onset in clinical settings. The current study sought to explore use and utility of retrospective ratings in adult outpatients. Aims were 1) to explore types of collateral raters and characterize their ratings and 2) to examine the clinical utility of collateral ratings.

**Methods:** Ninety-eight outpatients seeking an ADHD evaluation completed the Childhood Symptoms Scale (CSS), which includes 18 DSM-5 ADHD symptom items and related functional impairment questions. CSS collateral reports were obtained, along with demographic information, current behavior ratings, and semi-structured interviews to assess ADHD and other psychiatric conditions. T-tests were used to compare CSS rater types and correlations were performed to examine relationships between self and other ratings. Logistic regressions examined the contributions of collateral ratings to ADHD diagnosis.

**Results:** Collateral CSS ratings were most often completed by parents (72%, n=71); the remaining 28% were other family members, friends, or unidentified. Patients who submitted a parent CSS rating were significantly younger than patients who provided another collateral rater ( $p<.05$ ). Total ADHD symptom severity (parent:  $M=24.03$ , other:  $M=25.73$ ) and functional impairment scores (parent:  $M=9.24$ , other:  $M=8.77$ ) did not differ by collateral rater type, nor did symptom counts for inattention (parent:  $M=3.74$ , other:  $M=3.82$ ) or hyperactivity/impulsivity (parent:  $M=4.33$ , other:  $M=4.00$ ). ADHD symptom severity and functional impairment scores for self and collateral raters were significantly correlated ( $r$ 's ranged from .610 to .730,  $p$ 's $<.001$ ) both when analyzed as one group and separately by rater type. Despite high agreement between raters, self-ratings were significantly higher than collateral ratings for ADHD symptom severity (self-rating:  $M=27.97$ ; collateral rating:  $M=24.44$ ;  $p<.001$ ) and functional impairment scores (self-rating:  $M=10.73$ ; collateral rating:  $M=9.74$ ;  $p<.01$ ). When self and collateral retrospective ratings of ADHD symptom severity and functional impairment were entered as predictors of ADHD diagnosis, self-symptom ratings were the only significant predictor ( $p=.009$ )—collateral functional impairment approached significance ( $p=.06$ ). In a second logistic regression, current self and collateral symptom ratings were entered first and retrospective self-rating of symptom severity was entered next. After accounting for both current symptom ratings, retrospective self-rating scores positively predicted ADHD diagnosis ( $p=.004$ ).



**Conclusions:** Collateral reports of childhood ADHD symptoms and functional impairment do not differ across sources, and high agreement was found between self- and collateral retrospective ratings. Younger patients tended to use parents as collateral raters, whereas older patients tended to provide other collateral ratings. Collateral functional impairment ratings approached significance in a regression predicting diagnostic outcome, but collateral symptom ratings do not contribute to the model. Clinicians should consider the relative utility of obtaining collateral retrospective ratings.

## **F22. SELF- VERSUS COLLATERAL INFORMANT-REPORTED SYMPTOMS OF ADHD, ANGER-IRRITABILITY, AND IMPAIRMENT IN ADULTHOOD IN A LONGITUDINALLY FOLLOWED SAMPLE OF CHILDREN WITH ADHD**

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**Background:** This presentation will compare self- and collateral informant-reported symptoms of ADHD, anger/irritability (an ODD item subset), and associated impairment for older adults followed longitudinally since childhood. Children with ADHD underreport their symptoms and impairment, and this tendency continues into the early 20s. The systematic study of this tendency into later adulthood is under-researched, including lack of information regarding anger/irritability underreporting and associations with pertinent characteristics.

**Methods:** Using a sample of children research-diagnosed with ADHD in childhood ( $n = 99$ ) and interviewed in their 30s (mean age = 33.4 years,  $SD = 3.5$ ) from the Pittsburgh ADHD Longitudinal Study, the current study compared self-reported and collateral (91% parents; 9% romantic partner) informant-reported symptoms of ADHD, anger/irritability, and impairment based on standardized rating scales. Adults whose mean scores were lower than the informant report were compared across a range of demographic, personality, and task-measured variables.

**Results:** Self-reported scores of inattention, anger/irritability, and overall impairment were significantly lower than collateral-reported scores ( $p = 0.01-0.000$ ). Self-reported impulsivity/hyperactivity was not significantly different from the collateral informant-reported score. Compared with final symptom and impairment scores calculated from both reports (using the evidence-based “either-or” rule, taking the higher report at the item level), 49–77% of probands self-reported lower scores for ADHD symptoms overall, inattention, hyperactivity-impulsivity, anger/irritability, and impairment. Bivariate logistic regression analyses were conducted to test the association between underreporting ADHD symptoms/impairment and demographic predictors (age, gender, education, monthly income), facets of impulsive personality (lack of planning, lack of perseverance, negative urgency, positive urgency, sensation seeking), and contrasting measures of ADHD symptoms and impairment. Significant predictors at the bivariate level were retained for multivariate logistic analysis. Those with less education were significantly more likely to underreport their overall ADHD symptoms ( $b(SE) = 1.92(.90)$ ,  $p < .05$ ), inattention ( $b(SE) = 1.61(.80)$ ,  $p < .05$ ), and impulsivity/hyperactivity ( $b(SE) = 1.37(.67)$ ,  $p < .05$ ). Worse overall impairment was significantly associated with underreporting overall ADHD symptoms ( $b(SE) = .57(.17)$ ,  $p < .01$ ), inattention ( $b(SE) = .53(.15)$ ,  $p < .001$ ), impulsivity/hyperactivity ( $b(SE) = .45(.13)$ ,  $p < .01$ ), and anger/irritability ( $b(SE) = .53(.13)$ ,  $p < .001$ ). Worse symptoms of inattention significantly predicted underreporting overall impairment ( $b(SE) = 1.39(.56)$ ,  $p < .05$ ), as were worse symptoms of anger/irritability ( $b(SE) = .67(.33)$ ,  $p < .01$ ).

**Conclusions:** Collateral reports of ADHD symptoms continue to be important for assessing symptomatology and impairment in the fourth decade of life. Relying only on self-report could lead to underestimating symptom severity and impairment by one half to three-fourths of a standard deviation. The current study supports the continued need for improved methods of measuring ADHD symptoms across the lifespan and understanding when collateral informant report is crucial to obtain.

## **F23. THE VALIDITY OF ADULT – ONSET ADHD: A CRITICAL ANALYSIS**

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**Background:** Several recent population-based studies suggest that there may be a subgroup of adults who meet current symptom and impairment criteria for ADHD, but did not experience symptoms until adulthood (i.e., “adult-onset ADHD”). This suggests that the age of onset criterion may not be valid or that there is a need for an adult-onset subtype. Others have argued that these findings are related to flawed assessment of symptom onset or other environmental factors that mask symptoms, rather than lack of symptoms in childhood. This controversy leads to two considerations of import: if adult-onset ADHD is a valid diagnosis, we may be excluding a subgroup of individuals who would benefit from ADHD services, but do not currently meet diagnostic criteria for ADHD due to a possibly arbitrary age of onset criterion (i.e., false negative group); on the other hand, if adult-onset ADHD is not a valid diagnosis, disregarding the age of onset criterion may lead to incorrect or unnecessary evidence-based ADHD treatments and/or provision of unfair accommodations to individuals who should not qualify for services (i.e., false positive group). Given the gate-keeping nature of diagnosis to services (e.g., access treatment and accommodations) understanding the diagnostic validity of the age of onset criterion for ADHD is imperative to ensure appropriate access to these services. A theory-guided systematic review is needed to evaluate the quality of the current evidence to determine potential diagnostic validity of adult-onset ADHD and to provide future research directions.

**Methods:** A systematic review was conducted in Fall 2018 to examine and critically analyze the extant literature surrounding the diagnostic validity of adult-onset ADHD to answer the review question: Is adult-onset ADHD a valid psychiatric diagnosis? The Robins-Guze (1970) theoretical framework was used to determine if an observed clinical phenomenon is a valid psychiatric diagnosis. A modified Cochrane GRADE method was used to assess the quality of the existing empirical evidence. Specific inclusion criteria were: 1) An empirical study, 2) Examined new ADHD diagnoses in adults (i.e., age 18 and older), 3) Included measure of age of ADHD symptom onset, and 4) Written or translated into English. Specific exclusion criteria were: 1) Studies examining only “late-onset” ADHD as defined by onset post age 12 or unclear definition of “late-onset” and 2) Case studies. MeSH term searches were conducted in PubMed, PsycINFO, ERIC, Cinahl and Google Scholar.

**Results:** Seven studies examined the possibility of adult-onset ADHD as a valid psychiatric diagnosis with mixed conclusions. The rapidly emerging empirical literature on this topic has multiple methodological constraints that presently limit firm conclusions from being drawn.

**Conclusions:** The topic of adult-onset ADHD is generating considerable interest. Despite the great interest, the existing literature has multiple methodological flaws. Future adult-onset ADHD research should clarify how adult-onset ADHD is related to subthreshold ADHD and other associated conditions. Further investigating the age of onset criterion (DSM-5 ADHD Criterion B) represents a topic of great public health importance.

## **F24. MACHINE LEARNING CLASSIFICATION OF ATTENTION DEFICIT HYPERACTIVITY DISORDER USING STRUCTURAL MRI DATA**

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**Background:** Diagnosing ADHD requires a clinical evaluation of symptoms, which has been considered “subjective”. Recently, machine learning (ML) classifiers have been explored to develop objective methods of ADHD diagnosis using magnetic resonance imaging (MRI) biomarkers, yielding a wide range of accuracies of uncertain clinical significance.

**Methods:** We first reviewed previous literature seeking to develop clinically useful classifiers for ADHD using MRI data. Secondly, we used structural MRI (sMRI) data from the ENIGMA-ADHD Working Group (n = 3,377) to evaluate ML predictive accuracy for ADHD in childhood and adulthood. The dataset was balanced to control for age, sex, diagnostic group, and MRI acquisition site. We also used ML to test hypotheses about the continuity of child and adult ADHD. With the best models, we computed a continuous brain risk score (BRS) indexing the probability of being diagnosed with ADHD and evaluated our models’ sensitivity and specificity. Lastly, we computed a composite score indexing the importance of each brain region in the classification models.

**Results:** Our review shows that classification accuracies reported from studies using independent held-out test samples were significantly lower than accuracies reported from cross-validation (CV) samples. Using independent held-out samples for test in our study, we found that our models significantly discriminated ADHD and control samples for both children and adults, but the accuracies were modest (the area under the receiver operating characteristic curve (AUC): 63.8% and 56.5%, respectively). Including child samples in training data resulted in a significant increase in prediction accuracy for the adult ADHD (AUC 67.7%,  $X^2(1) = 5.31$ ,  $p=0.021$ ). For the child data, surface area measures were found to be the most important features (mean important score 0.250, 95%CI: 0.245, 0.255), followed by subcortical volumes (0.238, 95%CI: 0.220, 0.255) and cortical thickness measures (0.204, 95%CI: 0.199, 0.210). The same pattern held for the adult data.

**Conclusions:** Previous studies of ML in classification of ADHD that did not use a held-out test set have reported overly optimistic diagnostic accuracies. Our results suggest that clinically useful classification of ADHD may be possible with larger samples. In contrast to prior analyses of the ENIGMA-ADHD data, our work finds sMRI differences between adults with and without ADHD and shows that the sMRI brain differences between cases and controls seen in youth can also discriminate adults with and without ADHD. This provides additional evidence for the continuity of ADHD’s pathophysiology from childhood to adulthood.

## **F25. AVOIDANCE BEHAVIOR IN PATIENTS WITH COMORBID PTSD AND ADHD**

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**Background:** There is a paucity of research in Attention Deficit Hyperactivity Disorder (ADHD) comorbid with Post-traumatic Stress Disorder (PTSD) in adult psychiatric populations. Past research has found a significant increase in escape avoidance in ADHD

populations compared to healthy populations. Avoidance is a major criterion in the diagnosis of PTSD and is a significant factor in the maintenance of PTSD symptoms. Furthermore, ADHD has been linked as an independent risk factor for PTSD. To our knowledge, no previous study has specifically looked at avoidance behavior in an adult psychiatric population with a dual diagnosis of PTSD and ADHD.

**Methods:** To investigate this, a preliminary, retrospective study was conducted using psychiatric outpatient data collected by tertiary-care mood and anxiety clinic in Toronto, Canada. Patients (n=82) were referred to the clinic for various psychiatric concerns, including PTSD without ADHD (n=10) and PTSD comorbid with ADHD (n=19). PTSD and ADHD diagnoses were established using the clinical-structured Mini-International Neuropsychiatric Interview. The Impact of Events Scale – Revised: Avoidance Subscale scores were analyzed as an indicator of avoidance behavior in stressful situations. Data was analyzed using IBM SPSS Software.

**Results:** An independent sample t-test was conducted to determine a significant difference in mean scores between PTSD and PTSD-ADHD comorbid populations. A significant association was found between IES-R: Avoidance Subscale scores and PTSD-ADHD comorbid diagnosis  $F(1, 43) = 2.72, p = 0.009$ .

**Conclusions:** Our results revealed that in comparison to patients with PTSD without ADHD, patients with the PTSD and ADHD comorbidity had significantly higher scores on avoidance. As well, ADHD's inattention factor was also moderately associated with avoidance symptoms in PTSD.

Past research has implicated ADHD patients in avoidance behavior during CBT, which prevents active coping mechanisms, perhaps supporting our findings as well as suggesting a mechanism for understanding why the presence of these conditions together lead to increasing severity of prognosis. Furthermore, dysfunctional top-down regulation characteristic of populations with ADHD may explain increased avoidance behavior in patients with a dual diagnosis of PTSD and ADHD. Taken as a whole, our findings suggest how important it is to avoid the underdiagnosis and misdiagnosis of ADHD and particularly focus treatment of all comorbidities in PTSD.

## **F26. MATERNAL ADHD SYMPTOMS AND RISKS FOR PROBLEMATIC EATING BEHAVIOR IN CHILDREN**

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**Background:** ADHD during childhood is linked to dysregulated eating and obesity. One potential mechanism may be via parental ADHD symptoms, which have been linked to an array of negative outcomes for youth. However, the relationship between parental ADHD symptoms and early childhood eating patterns has not been previously studied. The current study used a community sample to examine the association between maternal ADHD symptoms and feeding practices as well as child eating behaviors.

**Methods:** The sample (N=211) was derived from an ongoing longitudinal study of women (mean age = 34.1 years, SD=5.76, 59% Black, 33.6% White, 7.5% Hispanic/Other) and children (mean age=5.7 years, SD=2.29, range=3-11, 47% male) recruited from the community. Maternal ADHD symptoms were measured via raw scores on the CAARS-Self-Report: Screening Version (CAARS-S-SV) Inattentive, Hyperactive/Impulsive, ADHD Index,

and ADHD Total subscales. The Child Feeding Questionnaire (CFQ)—a measure of parental practices, beliefs, and attitudes regarding child feeding—and the Child Eating Behavior Questionnaire (CEBQ), a measure of eating styles, were completed by mothers during a study visit. Child BMI was also calculated. Multiple linear regressions were run between CAARS-S-SV subscales and scores on the CFQ, CEBQ, and child BMI. Child age, gender, and child ADHD symptoms, measured via the Behavior Assessment System for Children (BASC), were examined as covariates.

**Results:** Controlling for relevant covariates, maternal scores on the CAARS-S-SV were predictive of higher scores on the CEBQ Emotional Over-Eating subscale (Inattentive:  $\beta=.18$ ,  $t(208)=2.47$ ,  $p=.01$ ; Hyperactive/Impulsive:  $\beta=.16$ ,  $t(208)=2.17$ ,  $p=.03$ ; ADHD Index:  $\beta=.19$ ,  $t(208)=2.61$ ,  $p=.01$ ; ADHD Total:  $\beta=.19$ ,  $t(208)=2.59$ ,  $p=.01$ ). ADHD Index subscale scores were also predictive of higher scores on the CEBQ Slowness in Eating subscale,  $\beta=.16$ ,  $t(208)=2.23$ ,  $p=.03$ . With regards to feeding patterns, higher scores on the Hyperactivity/Impulsivity,  $\beta=-.24$ ,  $t(208)=-3.29$ ,  $p=.001$ , ADHD Index,  $\beta=-.17$ ,  $t(208)=-2.28$ ,  $p=.02$ , and ADHD Total subscales,  $\beta=-.21$ ,  $t(208)=-2.280$ ,  $p=.006$ , predicted lower scores on the CFQ Monitoring subscale. In addition, higher scores on the ADHD Index subscale were significantly predictive of lower scores on the CFQ Perceived Responsibility subscale,  $\beta=-.20$ ,  $t(201)=-2.60$ ,  $p=.01$ , and scores on the Inattentive,  $\beta=-.14$ ,  $t(201)=-1.82$ ,  $p=.07$ , and ADHD Total subscales,  $\beta=-.13$ ,  $t(201)=-1.67$ ,  $p=.10$ , were associated at a trend level. Maternal ADHD symptoms were not significantly associated with child BMI.

**Conclusions:** Maternal ADHD symptoms—a known risk-factor for several different developmental outcomes for children—also appear to be associated with less optimal child eating and feeding behaviors. Specifically, greater maternal ADHD symptoms were associated with higher levels of emotional over-eating (e.g., “child eats more when worried”) as well as reduced parental monitoring (e.g., “How much do you keep track of the sweets your child eats?”) and parental perceived responsibility (e.g., “How often are you responsible for your child’s portion sizes?”). These findings align with previous research linking maternal ADHD symptoms to inconsistent parenting practices, decreased monitoring, and trouble sustaining attention in supervision. Though child BMI was not related to maternal ADHD symptoms, further analyses with a larger sample as well as measuring weight trajectories over time will be important to further clarify these trends.

## **F27. EXPLORING ATTENTION AND DRINKING BEHAVIORS IN COLLEGE STUDENTS: BASELINE CHARACTERISTICS**

Mariely Hernandez\*<sup>1</sup>, Sarah Scherrer<sup>2</sup>, Geneva Hidalgo<sup>2</sup>, Sarah O'Neill<sup>1</sup>

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**Background:** College is an especially vulnerable period for young adults because of the prevalence of high-risk drinking behaviors. Although college students with and without ADHD report comparable rates of alcohol use, those with ADHD report higher levels of negative alcohol-related outcomes. Alcohol expectancies and impulsivity may moderate negative alcohol-related outcomes. This study, currently under data collection, explores in a diverse urban sample, whether individuals who endorse more ADHD symptoms are (1) at greater risk for an alcohol use disorder (AUD); (2) report more negative alcohol-related outcomes than their peers despite comparable rates of alcohol use; and (3) whether impulsivity moderates these relationships.

**Methods:** As part of an ongoing two-part study, we present preliminary data from the part 1 survey ( $n=53$ , target  $N=500$ ) to characterize a diverse sample of full-time undergraduate college students aged 18-25 attending a large, urban college in the North Eastern US. Part 1

participants completed a background demographic questionnaire, the Alcohol Use Disorders Identification Test (AUDIT), the Drug Use Disorders Identification Test (DUDIT), 6 screener questions from the Adult ADHD Self-Report Scale (ASRS v1.1), 25 childhood ADHD symptom questions of the Wender-Utah questionnaire, Barkley's Deficits in Executive Function-Short-form survey (BDEFS), the Barratt Impulsivity Scale (15-item version; BIS15), and the College Drinking Influences Scale (CDIS). Summary scores of the ASRS v1.1 screener were derived from the ASRS DSM-5 conversion algorithm.

**Results:** Preliminary sample demographic characteristics are as follows: 77.4% (n=41) were female, 94% (n=50) were between 18 and 21 years of age. A diverse sample, 30.2% (n = 16) identified racially as Asian, 26.4% (n = 14) as Black/Afro-Caribbean, 20% (n = 11) as White, and 1.8% (n = 1) as Native American/Pacific Islander. Thirty-two percent (n = 17) separately ethnically identified as Hispanic/Latinx. The majority lived off-campus (89%, n=48) and with their families (n=45). Sixty percent (n=32) affiliated with a religious community, of which 65.6% (n=21) noted that their faith has a great influence on their daily life. Regarding alcohol and drug use, 60% (n=32) reported ever having a full drink of alcohol, and 32% (n=17) ever used any illegal drugs. Nearly 38% (n=20) reported definite or probable family psychiatric history.

Mean scores for survey data include: ASRS (n=52; M=7.6, SD= +3.54); Wender-Utah (n=50; M= 16.04, SD=+ 14.5); AUDIT (n=51; M= 1.82, SD= + 2.72); BIS (n=50; M=26.88, SD= + 7.20); BDEFS (n=51; M= 31.92, SD= + 10.24).

Nearly 19% (n=10) scored > or = 11 on the ASRS, suggesting a likelihood of ADHD. Independent samples t-tests between those who scored above and below 11 on the ASRS revealed significant differences in mean scores on the Wender-Utah, BIS15 and BDEFS survey data (p<.0001), though not for alcohol use data on the AUDIT or drug use data on the DUDIT (based on Chi-Square analyses).

**Conclusions:** These preliminary data depict a racially diverse sample of commuter college students with generally lower than average alcohol and drug use, despite elevated ADHD symptom scores. It is possible that religious affiliation and living with family may serve as protective factors for students who might be otherwise at risk for experiencing negative consequences related to alcohol and substance use. These preliminary findings do not include data on the consequences of alcohol use, as these measures are collected during the Part 2 assessment.

## **F28. ASSOCIATIONS AMONG CHILDREN'S ADHD SEVERITY, PARENTING STRESS AND SOCIOECONOMIC STATUS ACROSS EARLY CHILDHOOD**

Ramya Jayanthi\*<sup>1</sup>, Sarah O'Neill<sup>1</sup>, Shelagh Mahbubhani<sup>1</sup>, Elias Collado<sup>1</sup>, Khushmand Rajendran<sup>2</sup>, Jeffrey Halperin<sup>3</sup>

<sup>1</sup>City College of New York, <sup>2</sup>City University of New York, <sup>3</sup>Queens College

**Background:** Mothers of children with ADHD report greater parental stress than mothers of typically developing children (Byrne et al., 1998), and cross-sectional studies indicate that greater severity of children's ADHD symptoms is associated with higher parenting stress (Podolski and Nigg 2001; Theule et al. 2010). How these factors affect each other across early childhood has not yet been explored. Furthermore, how socioeconomic status may impact these relations has yet to be explored, despite research showing that SES is independently negatively related to both ADHD severity (e.g., Russell et al., 2016) and parent stress (e.g., Conger & Donnellan, 2007).

**Methods:** This study explored the reciprocal relations between parenting stress and children's ADHD severity over three years, as well as the effect of socioeconomic status (SES) on parenting stress and child ADHD severity at baseline. It was hypothesized that: (1) children's ADHD severity and parenting stress would be positively related across time; and (2) baseline SES would be negatively related to both parenting stress and child ADHD severity at baseline. Method: Preschoolers (N=216, mean age=4.3 years, SD=.47; 73% males) were assessed annually from 3-4 (T1) through 5-6 years of age (T3). At each time point, teachers completed the ADHD Rating Scale–IV to measure ADHD severity while mothers completed the Parenting Stress Index, Fourth Edition. SES was assessed at T1 using several measures: maternal and paternal highest education level, income-to-needs ratio (Barch et al., 2016), marital status and parental occupational prestige (Nakao & Treas, 1994). A cross-lagged panel analysis was carried out in AMOS investigating the associations among child ADHD Severity and Parenting Stress at three time points: 3-4 (T1), 4-5 (T2), and 5-6 years (T3). The relation of SES to child ADHD Severity and Parenting Stress at T1 was also assessed. A latent variable comprising the five indicators of SES was created and used in the analysis.

**Results:** A non-significant chi-square, Comparative Fit Index (CFI = .99), and Root Mean Square Error of Approximation (RMSEA = .03 [90% CI = .00, .06]) were considered to be indices of good fit (Hu & Bentler, 1999; Kline, 2005). T1 SES was negatively related to both T1 child ADHD severity and maternal parenting stress ( $\beta = -.43$  and  $-.02$ , respectively;  $p < .05$ ), respectively. After controlling for T1 SES, parenting stress at 3-4 years was positively associated with child ADHD severity one year later (4-5 years) ( $\beta = .23$ ;  $p = .05$ ), which in turn was positively associated with parenting stress a year later (5-6 years) ( $\beta = .07$ ;  $p = .03$ )

**Conclusions:** ADHD behaviors begin to emerge during preschool and thus parents are first exposed to them, which may be why parenting stress has a prominent role on later behavior during this period. That ADHD behaviors at ages 4-5 years appear to increase later parenting stress may reflect how parents are affected by children's worsening behavior as they transition to school.

## **F29. ADHD SYMPTOM SEVERITY AND PARENTAL SELF-EFFICACY IN A MIXED CLINICAL SAMPLE**

Corina Zisman\*<sup>1</sup>, Natalie Ridgely<sup>1</sup>, Erin Jones<sup>1</sup>, Lisa Jacobson<sup>2</sup>, Alison Pritchard<sup>1</sup>, T. Andrew Zabel<sup>1</sup>

<sup>1</sup>Kennedy Krieger Institute, <sup>2</sup>Johns Hopkins School of Medicine, Kennedy Krieger Institute

**Background:** Parental self-efficacy is broadly conceptualized as a parent's perception of their ability to successfully influence their child's development through their parenting approaches (Jones & Prinz, 2005). Research has suggested linkage between a parent's self-perceived ability to manage their child and a child's overall functioning, health, and behavior (Hack et al., 2016; Breaux et al., 2018). In addition to positive effects on a child's development, parental self-efficacy also mediates family distress and parent mental health (Weiss et al., 2013). Attention Deficit/Hyperactivity Disorder (ADHD) is a developmental disorder estimated to affect over 5 percent of children worldwide and is characterized by high levels of inattention, hyperactivity and impulsivity (American Psychiatric Association, 2017). The aim of this study was to determine if increased child ADHD symptom severity is associated with reduced parental self-efficacy. Such a relationship would have implications for planning and allocation of parental support services, given the association between parental self-efficacy and parental mental health.

**Methods:** Parents of children with a diagnosis of ADHD seen in an outpatient clinic between January 2017 to September 2018 (N = 155) provided responses to a 13-item (5-point Likert

scale) parent self-efficacy questionnaire prior to assessment. Items queried parents' confidence in their ability to address their children's needs across a variety of domains (e.g., "I am confident in my ability to help my child manage his/her behavior"). A core set of items were modeled after Austin et al. (2017), and the remaining items were theoretically derived. Previous evaluation of these data has identified three factors of parent self-efficacy relating to parents' self-perceived ability to 1) understand, 2) manage, and 3) advocate for their children (Jones et al., 2018). Prior to their child's appointment, parents also completed ratings of ADHD symptom severity as part of a larger developmental history form (ADHD Rating Scale-5; DuPaul et al., 2016).

**Results:** Regression analysis found a significant negative relationship between parents' ratings of child ADHD symptom severity and their perceived ability to manage their child's behavior. Holding child's age constant, higher parental self-efficacy ratings for management of condition were associated with lower symptom severity ratings for total symptoms ( $b = -.42$ ,  $t(573) = -7.24$ ,  $p < .001$ ), inattentive symptoms ( $b = -.36$ ,  $t(573) = -6.80$ ,  $p < .001$ ), and hyperactive/impulsive symptoms ( $b = -.27$ ,  $t(572) = -5.76$ ,  $p < .001$ ). A less robust negative correlation was found between parent ratings of ADHD symptom severity and their ability to understand their child's condition, and no significant correlation was found between child ADHD symptom severity ratings and parental efficacy around advocating for their child.

**Conclusions:** Results of this preliminary study suggest an association between child ADHD symptom severity and parental self-efficacy ratings specific to behavioral management of the child. This is important for clinicians to note when working with families, as symptom severity might be a predictor of parental distress and vulnerability to mental health issues.

### **F30. PHQ-9 REDUCTION AND RELIEF FROM DEPRESSIVE SYMPTOMS WITH PSYCHOSTIMULANT MONOTHERAPY**

Jesse McClelland\*<sup>1</sup>, Kimi Hashimoto<sup>1</sup>, Joshua Potter<sup>1</sup>

<sup>1</sup>Psychiatry Northwest LLC & TMS Washington

**Background:** ADHD is frequently co-morbid with dysthymia or major depressive disorder but is commonly undiagnosed or untreated because the established algorithm in psychiatry dictates that providers first address a major depressive episode before addressing ADHD in patients with these comorbidities. ADHD often precedes the onset of depression, significantly contributing to depressive symptoms in adults, despite ADHD being often overlooked and untreated. Many adults have tried standard treatment for depression with no response or unwanted side effects that may worsen their underlying ADHD. In this open labeled study comprised of patients undergoing treatment for MDD or ADHD, we use an unconventional treatment methodology by treating clinical depression by addressing ADHD symptoms first. ADHD is more rapid to treat so treatment of ADHD first may also determine if other target symptoms remain. This study's objective is to examine if treating underlying ADHD with stimulant monotherapy will also treat a patient's depression symptoms, and to what extent of clinical significance.

**Methods:** In a randomly selected sample of 250 adult patients with no medication and baseline PHQ-9 scores of 8+, we examined patients' PHQ-9 scores once they were stable on an extended release ADHD medication for more than 3 months. Exclusion criteria: diagnosis of bipolar disorders, psychotic disorders, contraindication to taking stimulants due to pre-existing medical conditions, and substance abuse. A significant clinical response entails that patients' depressive symptoms and rating on the PHQ-9 is reduced by at least 50%.

**Results:** A paired-samples t-test was conducted on SPSS to evaluate our hypothesis that treating ADHD with psychostimulants, i.e. Concerta, Mydayis, Adderall XR, can reduce



depressive symptoms. The test was significant,  $t(250) = 26.3, p < .001$ , and the results support the research hypothesis. The average PHQ-9 at baseline was 15.22 (SD = 4.6) and after the intervention of ADHD medication, the mean PHQ-9 was 5.95 (SD = 4.9). On average, depressive symptoms decreased by 61% in patients who were concurrently treating their depression and ADHD with psychostimulants, indicating a significant clinical response in depressive symptoms. Our results demonstrate that ADHD treatment can also resolve most, if not all depression symptoms without further necessity for antidepressants.

**Conclusions:** From our findings, we conclude that treating underlying ADHD as a first-line intervention for dysthymia and MDD is clinically effective and safe. Patients can establish an effective, stable medication regimen in 3 months to resolve all target symptoms with minimal side effects unlike the standard treatment intervention which may take significantly longer for patients to notice any improvements due to poor tolerance and response to antidepressants. Patients diagnosed with moderate to severe MDD had significant clinical improvement in symptoms by treatment of ADHD medication, nearly to the point of full remission. Our results may indicate that depression in the context of ADHD can be caused by improper or lack of treatment of ADHD. When we apply this unconventional methodology and treat patients' ADHD with psychostimulants as a first-line of treatment rather than the standard intervention of antidepressants, we find that there is no depression symptoms left to treat. Providers seeking to adopt this methodology should closely monitor patients' dosing to prevent abuse of a controlled substance, tolerance, or any negative side effects.

### **F31. WOMEN AND ADHD FUNCTIONAL IMPAIRMENTS: BEYOND THE OBVIOUS**

Noelle Lynn\*<sup>1</sup>

<sup>1</sup>Grand Valley State University

**Background:** Functional impairments, which are the manifestation of the disability and its symptoms in daily life, have been found to be the root cause of many negative life outcomes. Because of the structure of the DSM criteria, much of the literature assumes that functional impairments are the direct by-product of the core ADHD symptoms of inattention, impulsivity, and hyperactivity. Yet, this limited view of the scope of ADHD may cause researchers and practitioners to overlook areas of major impairment that are not easily explained by core symptoms. These impairments include emotional dysregulation, lack of ability to self-direct, stay motivated, and respond consistently to stimuli, dysfunctional cognition, and limited working memory (Faraone et al., 2000; He, J. A., Antshel, K. M., Biederman, J., & Faraone, S. V, 2015; Smyth et al., 2016; Strohmeier, C. W., Rosenfield, B., DiTomasso, R. A., & Ramsay, J. R, 2016). According to the research reviewed, diagnostic status does not impact the experience of functional impairments. ADHD functional impairments can be and are found in those who have not been clinically diagnosed, but who meet the basic criteria for a DSM V diagnosis (Abel, S. L., Johnston, J. A., Adler, L. A., & Swindle, R. W, 2007). This indicates that functional impairments caused by ADHD are not a by-product of the diagnosis but instead are a pervasive and life inhibiting for all those with this disability.

While the existence and external impacts of functional impairments have been validated in the literature, there is little discussion of how functional impairments affect the lived, internal, experiences of adult women.

**Methods:** Through 15 semi-structured interviews, women from around the United States will share about how functional impairments show up in their lives, how their minds, bodies, and emotions respond, and how these occurrences influence their outlook on the world around

them. These women were selected from a survey of women who all took the Weiss Functional Impairment Rating Scale. Each of the 15 women has a distinct Weiss Functional Impairment Rating Scale scores, so as to have a diversity of intensity represented in the sample.

**Results:** This study is currently underway. It is expected that at least preliminary, if not full, findings, will be ready by the APSARD 2019 conference.

**Conclusions:** The study of the lived experiences of women with ADHD is essential to improving the care they are offered. Through this study, a better understanding will be gained of the many ways functional impairments impact women's lives.

### **F32. GENES AND BRAIN CELL TYPES LINKED WITH SELECTIVE NEURONAL VULNERABILITY IN ADHD**

Jonathan Hess\*<sup>1</sup>, Jameson Patak<sup>1</sup>, Stephen Faraone<sup>1</sup>, Stephen Glatt<sup>1</sup>

<sup>1</sup>SUNY Upstate Medical University

**Background:** A series of large multi-site mega-analyses of structural brain imaging data led the Enhancing Neuroimaging Genetics through Meta-analysis (ENGIMA) Network found several brain regions that show significant volumetric reductions in individuals diagnosed with attention deficit hyperactivity disorder (ADHD). Some regions showed substantially greater loss than others, which might be an indicator of selective neuronal vulnerability (SNV).

**Methods:** We hypothesized spatial variation in gene expression levels across brain regions may explain this phenomenon. To test this hypothesis, we devised an approach to that used RNA-sequencing data the Allen Brain Atlas to uncover gene sets and brain cell types associated with SNV in ADHD. We targeted gene sets based on hypotheses derived from prior work.

**Results:** We identified statistically significant correlations between volumetric loss in ADHD and expression levels of genes involved in reactive oxygen, autophagy, and apoptosis. Furthermore, we uncovered a significant correlation between abundance of three brain cell types (microglia, radial glia, and floorplate derived neuronal progenitor cells) with brain volumetric changes associated with ADHD. Results from conditional regression models suggested that the effect of brain cell abundance on volumetric loss in ADHD may be mediated by gene expression levels.

**Conclusions:** We concluded that gene expression levels influence brain cell abundance, which in turn mediates liability for ADHD.

### **F33. ASSOCIATION BETWEEN DRD4 METHYLATION AND RESPONSE TO METHYLPHENIDATE AND PLACEBO IN CHILDREN WITH ADHD**

Weam Fageera\*<sup>1</sup>, Boris Chaumette<sup>2</sup>, Natalie Grizenko<sup>3</sup>, Sarojini M. Sengupta<sup>3</sup>, Ridha Joobar<sup>3</sup>

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**Background:** The study of the epigenetic basis for the individual variation in drug response, is an area that has gained much interest recently. Indeed, epigenetic variations may provide another level of explanation for inter-individual variations in drug response that cannot be accounted for on the basis of genetic polymorphism. This study aims to examine the association between DNA methylation of DRD4 gene and response to methylphenidate and placebo in children with ADHD.

**Methods:** 212 children with ADHD (6-12 years) participated in a randomized, double-blind, placebo-controlled crossover trial. Placebo response (PR) was calculated as the difference in

Conners' parents' and Conners' teachers' score at baseline and during placebo week. Medication response (MR), on the other hand, was calculated as the difference between placebo week and active medication week. DNA methylation of CpG sites in DRD4 was examined for association with MR and PR using spearman's correlation analysis.

**Results:** According to the parents' evaluation, one CpG located in the DRD4 showed a highly significant correlation with PR ( $r = -.263$ ,  $P=0.001$ ) and MR ( $r = -.180$ ,  $P=0.009$ ). Two other CpGs were associated with PR according to teachers' evaluation ( $r = -.168$ ,  $P=0.019$ ;  $r = -.142$ ,  $P=0.045$ ).

**Conclusions:** These preliminary results could provide evidence for the involvement of the epigenetic variation of DRD4 in modulating the response to treatment in ADHD.

### **F34. NEURAL MECHANISMS UNDERLYING THE THERAPEUTIC ACTIONS OF PS-OMEGA-3 FATTY ACID SUPPLEMENTATION IN ADULTS WITH ADHD**

Kurt Schulz<sup>\*1</sup>, Beth Krone<sup>1</sup>, Lenard Adler<sup>2</sup>, Stephen Faraone<sup>3</sup>, Jeffrey Newcorn<sup>4</sup>

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**Background:** The reluctance of patients to rely on pharmacological treatments for attention-deficit/hyperactivity disorder (ADHD) has increased interest in alternative therapies, such as omega-3 fatty acid supplementation. Meta-analyses have revealed small but significant effects of omega-3 fatty acid supplementation on symptoms of ADHD, and possibly emotional lability. These diet-derived fatty acids influence neuronal membrane fluidity and phospholipid composition, which can alter the structure and function of embedded proteins, and thereby may influence dopamine neurotransmission. However, little is known about the mechanisms by which omega-3 fatty acids exert their therapeutic effects for ADHD. This study tested changes in brain activation related to clinical improvement with omega-3 fatty acid supplementation in adults with ADHD.

**Methods:** Seventy-eight adults with ADHD were scanned twice with event-related functional magnetic resonance imaging while performing an emotional go/no-go task before and after 16 weeks of omega-3 fatty acid supplementation ( $n=23$ ) or 8 weeks of placebo lead-in followed by 8 weeks of omega-3 fatty acid supplementation ( $n=27$ ) or placebo ( $n=28$ ). The current study used an enrichment design to restrict analyses to the 31 of 55 (56%) participants who did not respond to placebo during the lead-in period. Whole-brain activation for affective response inhibition was regressed on clinical response with age, sex, and baseline ADHD severity as covariates.

**Results:** Following placebo lead-in, 8 weeks of omega-3 supplementation ( $n=17$ ) was associated with slightly greater clinical improvement than 8 weeks of placebo ( $n=14$ ) ( $p<0.05$ ). Changes in response execution and inhibition on the go/no-go task did not differ between the two groups. Clinical improvement for omega-3 fatty acid supplementation was associated with gains in task-related activation in pre-supplementary motor area (pre-SMA) and premotor cortex and reductions in caudate nucleus and precuneus activation compared to placebo ( $p<0.001$ ,  $kappa=50$  voxels).

**Conclusions:** These results provide preliminary evidence that inhibitory mechanisms in caudate nucleus and frontally-based visuomotor integration and motor programming processes contribute to the therapeutic actions of omega-3 supplementation in adults with ADHD. These changes in brain activation suggest that clinical improvement for omega-3 supplementation may involve dopaminergic and non-dopaminergic effects.

### **F35. THE EFFICACY OF PHOSPHATIDYLSERINE IN THE TREATMENT OF PEDIATRIC ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): A SYSTEMATIC REVIEW AND META-ANALYSIS**

Alisha Bruton\*<sup>1</sup>, Joy Nauman<sup>1</sup>, Angela Senders,<sup>1</sup> Douglas Hanes<sup>1</sup>, Melissa Gard<sup>1</sup>

<sup>1</sup>NUNM

**Background:** ADHD is one of the most commonly diagnosed psychiatric conditions of childhood, and can persist into adulthood with numerous adverse health outcomes. Many children do not receive standard-of-care stimulant medication due to medication side effects or lack of effectiveness, and integrative therapies warrant investigation.

**Methods:** To examine the evidence for effectiveness of phosphatidylserine supplementation for symptoms of ADHD in children, we conducted a systematic review and meta-analysis. Study participants were children <18 years old with ADHD. Intervention was phosphatidylserine supplementation in any dose/duration, and control was placebo, wait list, or standard of care. Outcome measures were validated scales of ADHD symptoms. All study designs were included in the narrative review, but only trials were included in the meta-analysis.

**Results:** Six studies met inclusion criteria for the narrative review (n=1064), and four studies for the meta-analysis (n=246). We found very low quality evidence that phosphatidylserine was significantly more effective than placebo in reducing ADHD symptoms (effect size=0.63, 95% CI= 0.01,1.24). In a priori subgroup analyses, we found low quality evidence that phosphatidylserine was more effective than placebo in improving symptoms of inattention (ES=0.36, 95% CI=0.07,0.64) but did not result in significant improvements in symptoms of hyperactivity/impulsivity (ES=0.55, 95% CI=-0.21,1.31).

**Conclusions:** Phosphatidylserine may be effective for reducing symptoms of ADHD in children, particularly symptoms of inattention. High quality research in this area is warranted. Future trials should be randomized, controlled, and adequately powered.

**Registration:** The protocol for this review is registered in the PROSPERO database, #CRD42018093188.

Saturday, January 19, 2019

Poster Session II with Lunch

12:30 p.m. - 2:30 p.m.

Exhibit Hall C

**S1. A PHARMACOKINETIC STUDY OF METHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES (APTENSIO XR®) IN MALE AND FEMALE PRESCHOOL CHILDREN 4 TO UNDER 6 YEARS OF AGE WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER UNDER FED. CONDITIONS**

Akwete Adjei\*<sup>1</sup>, Inder Chaudhary<sup>1</sup>, Nathan Teuscher<sup>2</sup>, Ed Freshwater<sup>2</sup>, Scott Kollins<sup>3</sup>, Americo Padilla<sup>4</sup>, Robert J. Kupper<sup>1</sup>

<sup>1</sup>Rhodes Pharmaceuticals L.P., <sup>2</sup>Certara, <sup>3</sup>Duke University, <sup>4</sup>Niklaus Children's Hospital

**Background:** Methylphenidate (MPH) is the most commonly prescribed medication for the treatment of attention-deficit/hyperactivity disorder (ADHD) in preschool children, even though it does not have Food and Drug Administration (FDA) approval for use in children under 6 years of age. There is an identified need for pharmacokinetic studies of MPH formulations in preschool children.

**Methods:** This was a single-dose, one-period, multi-center, pharmacokinetic study in preschool children 4 to < 6 years old in fed state previously diagnosed with ADHD, in which each child received a single oral dose of MPH extended-release capsule (MPH-MLR) sprinkled over apple sauce. Each child's administered dose was equivalent to his or her previously prescribed daily dose of MPH prior to enrollment in the study.

Blood samples for measurement of MPH concentrations were obtained pre-dose, and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours post dose. A nonlinear mixed-effects model was used to derive pharmacokinetic (PK) values for analysis: peak plasma concentration (C<sub>max</sub>), area under the curve (AUC), half-life (t<sub>1/2</sub>), clearance (CL) and volume of distribution (V<sub>d</sub>).

**Results:** Dose normalized MPH exposures, C<sub>max</sub>/Dose and AUC<sub>0-t</sub>/Dose were similar across doses. The results were integrated into a pharmacostatistical population PK model previously described for MPH-MLR in children 6 to 10 years of age to identify new covariates deemed important in preschool children. The final population PK model included 2 covariates, body weight on apparent CL and age group on the apparent V<sub>d</sub>. There was no gross bias in the residuals and visual predictive check (VPC) plots showed good agreement between the observed and predicted quantiles suggesting the final model accurately predicts the observed data. The VPC plots showed greater variability in the group 6 to 12 year-olds compared to the 4 to <6 year-olds, and CL increased with increasing body weight in a greater than allometric manner. Children in the 4 to <6 years group had a smaller V<sub>d</sub> than children in the 6 to 12-year-old group, the parameter estimates being similar for both groups, the only exception being the addition of the covariate for age group. Weight-normalized CL/F values were comparable across dose groups, and mean estimates of V<sub>z</sub>/F increased with age, while dose-normalization decreased differences across age groups, with the exception of the 4 to <6 age group, which had higher values.

**Conclusions:** Pharmacokinetics of MPH-MLR in preschool children demonstrated, for the first time, the biphasic absorption profile described earlier in older children and adults. The PK profile of MPH-MLR is similar between children with ADHD aged 4 to <6 years and those 6 to 12 years, except for a lower V<sub>d</sub> for preschool children. Dose-normalized maximum and total methylphenidate exposure, as measured by C<sub>max</sub>/Dose and AUC<sub>0 t</sub>/Dose, were similar across doses. AUC<sub>0 inf</sub>/Dose was similar for 15 mg and 20 mg methylphenidate doses and was lower after 20 mg compared to that after the 10 mg dose. The 95% confidence intervals calculated for methylphenidate CL/F/kg geometric mean fell entirely within the target confidence interval range of 60% to 140%. MPH-MLR was well tolerated in preschool children suggesting it could be a useful treatment option for children with ADHD 4 years of age and older.

**S2. A PHASE 4, OPEN-LABEL, MULTICENTER, SINGLE-DOSE STUDY OF THE PHARMACOKINETICS OF A NOVEL AMPHETAMINE EXTENDED-RELEASE ORAL DISINTEGRATING TABLET FORMULATION (AMP XR-ODT™) IN PRESCHOOL-AGED CHILDREN**

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**Background:** A third of children in the US with ADHD are diagnosed during the preschool years (<6 years old [y.o.]). Despite few ADHD medications indicated for use in this age group and limited pharmacokinetic (PK) and controlled efficacy/safety studies, pharmacotherapy is used in ~18% of preschoolers. In response to an FDA request for additional data in this age group, the PK profile of AMP XR-ODT, an amphetamine (AMP) extended-release orally-disintegrating tablet approved for use in patients  $\geq 6$  y.o., was assessed in children 4–5 y.o.

**Methods:** Eligible children 4 to <6 y.o. with a confirmed DSM-5 ADHD diagnosis were administered AMP XR-ODT 3.1 mg without food after a 10-h overnight fast. Blood samples were drawn pre-dose and serially up to 24 h post-dose and analyzed for d-AMP and l-AMP with a validated liquid chromatography tandem mass spectrometry assay. PK parameters for total exposure (AUC<sub>0–inf</sub>), exposure from time 0 to the last measurable plasma concentration (AUC<sub>0–T</sub>), maximum plasma concentration (C<sub>max</sub>), time to C<sub>max</sub> (T<sub>max</sub>), half-life (t<sub>1/2</sub>), volume of distribution (V<sub>z</sub>/F), and clearance (CL/F) for d- and l-AMP were calculated using non-compartmental methods. Safety was also assessed.

**Results:** Fifteen children (4 y.o., n = 6; 5 y.o., n = 9; 60.0% male) were included in the PK and safety analysis; 14 completed the study and 1 did not complete the final 24 h blood draw. For d- and l-AMP, mean AUC<sub>0–inf</sub> was 315.2 and 104.4 h\*ng/mL, AUC<sub>0–T</sub> was 296.0 and 96.8 h\*ng/mL, C<sub>max</sub> was 23.0 and 7.0 ng/mL, T<sub>max</sub> was 4.0 and 4.3 h, t<sub>1/2</sub> was 8.0 and 9.2 h, V<sub>z</sub>/F was 75.9 and 84.1 L, and CL/F was 7.0 and 6.8 L/h, respectively. Two subjects (13.3%) experienced 5 treatment-emergent adverse events: tachycardia (n = 2), neutropenia, increased alanine aminotransferase, and increased aspartate aminotransferase (n = 1 each), all of which, including both events of tachycardia, were mild and resolved without treatment.

**Conclusions:** AMP XR-ODT was generally well-tolerated in preschool-aged children, and the low dose resulted in detectable plasma AMP concentrations over 24 h. When PK data from this study is compared with previously published PK data for 18.8 mg AMP XR-ODT in 6–7 y.o. children with ADHD, elimination half-life is about 1–2 h shorter and d- and l-AMP T<sub>max</sub> were similar, suggesting comparable absorption.

### **S3. IMPROVEMENTS IN AT-HOME FUNCTIONAL IMPAIRMENT WITH DR/ER-MPH IN CHILDREN WITH ADHD: POST HOC ANALYSIS OF BSFQ AND PREMB-R BY NORM-REFERENCED CUT-OFFS**

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**Background:** In a pivotal phase 3 trial in children with attention-deficit/hyperactivity disorder (ADHD), evening-dosed HLD200, a delayed-release and extended-release methylphenidate (DR/ER-MPH), significantly improved ADHD symptoms and reduced at-home functional impairment versus placebo, as measured by two validated rating scales—the Before School Functioning Questionnaire (BSFQ) and the Parent Rating of Evening and Morning Behavior Scale–Revised (PREMB-R). There has been an increased focus on assessing ADHD-related functional impairment, a consequence of ADHD symptoms (e.g., missing breakfast because of

distractibility). Recently, age-adjusted cut-offs for the BSFQ and the PREMB-R morning (PREMB-R AM) and evening (PREMB-R PM) subscales were determined from a sample of 1200 representative US youth (6–17 y) to define severity levels of at-home functional impairment: screening risk (80th percentile), mild (90th percentile), moderate (93rd percentile), and severe (98th percentile). In this post hoc analysis, these age-adjusted, norm-referenced cut-offs were applied to BSFQ and PREMB-R AM/PM outcomes to help interpret changes in at-home functional impairment severity with DR/ER-MPH and placebo treatment.

**Methods:** Data were analyzed from a randomized, double-blind, multicenter, placebo-controlled, phase 3 trial of DR/ER-MPH in children (6–12 y) with ADHD (NCT02520388). Total BSFQ, PREMB-R AM, and PREMB-R PM scores were evaluated using the age-adjusted, norm-referenced cut-offs to determine the severity of at-home functional impairment at baseline and following three weeks of treatment. Comparisons between treatment groups in proportions and distributions of BSFQ, PREMB-R AM, and PREMB-R PM scores at baseline and Week 3 by norm-referenced cut-offs were performed. Proportions of participants with any severity of at-home functional impairment that “normalized” (i.e., below screening risk) after three weeks of treatment were also determined.

**Results:** Most participants at baseline were at or above screening risk for at-home functional impairment by norm-referenced cut-offs in both DR/ER-MPH and placebo groups (BSFQ: 98% and 96%, PREMB-R AM: 86% and 77%, PREMB-R PM: 94% and 91%, respectively). A considerable proportion of participants had severe at-home functional impairment in DR/ER-MPH and placebo groups at baseline (BSFQ: 62% and 64%, PREMB-R AM: 38% and 28%, PREMB-R PM: 47% and 41%, respectively). After three weeks, both treatment groups experienced substantial improvements in at-home functional impairment; however, improvements were more pronounced with DR/ER-MPH treatment versus placebo across all severity levels. Of the participants with at-home functional impairment of any severity at baseline (i.e., mild or greater), a greater proportion achieved “normalized” scores after three weeks of treatment with DR/ER-MPH versus placebo (BSFQ: 66% vs 39%, PREMB-R AM: 72% vs 40%, PREMB-R PM: 43% vs 26%, respectively).

**Conclusions:** Norm-referenced percentile cut-off points for BSFQ and PREMB-R can be used as a helpful guide for clinicians in determining the severity of ADHD-related at-home functional impairment among youth and for monitoring treatment effects. In this post hoc analysis of a phase 3 pivotal trial, three weeks of treatment with DR/ER-MPH resulted in more pronounced improvements across all severity levels of at-home functional impairment and more participants achieving “normalized” scores on the BSFQ and PREMB-R AM/PM versus placebo.

#### **\*\*S4. A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PLACEBO-CONTROLLED, CROSSOVER, SAFETY AND EFFICACY STUDY OF CENTANAFADINE SUSTAINED-RELEASE (CTN SR) IN ADULTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)**

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**Background:** To evaluate the efficacy and safety of centanafadine sustained-release (CTN SR) vs. placebo in adults with ADHD using the clinician-completed ADHD Rating Scale IV (ADHD-RS-IV).

**Methods:** Subjects 18 to 60 years of age, inclusive, who met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5®) diagnostic criteria for a primary diagnosis of ADHD, were screened for enrollment into study (NCT02547428). Subjects had to have an ADHD Rating Scale IV (ADHD-RS-IV) score of  $\geq 28$  at baseline, no other major medical or current psychiatric comorbidity, and a minimum score of 4 on the CGI-S.

Subjects were randomized to a 7-week double-blind crossover treatment period, with 3 weeks of CTN SR or placebo, one-week washout, and 3 weeks of either placebo or CTN SR with a target dose of 400-800 mg.

**Results:** A total of 117 subjects were screened from 4 study sites, 85 were eligible to be randomized: 42 to CTN SR/Placebo and 43 to Placebo/CTN SR sequence. 71% of subjects (60/85) completed the study; the safety population included 79 subjects who received at least one dose of CTN SR. CTN SR met its primary endpoint of a significant decrease in symptoms from baseline compared with placebo. The least square mean difference between CTN SR and placebo on the ADHD-RS-IV was -8.1 (95% CI [-11.0, -5.1]; effect size -0.66,  $p < 0.001$ ). The most frequently experienced treatment-related AEs were decreased appetite in (24.1%), headache (22.8%), and nausea (20.3%). No deaths or SAEs occurred within the study. A total of 11 (10.1% of subjects discontinued from CTN SR due to an adverse event.

**Conclusions:** Based on the promising safety and efficacy of CTN SR, adult and pediatric Phase 3 programs for centanafadine are planned for treatment of ADHD.

## **S5. Comparative Analysis of the Efficacy of Lisdexamfetamine and Extended-Release Methylphenidate in Adolescents With ADHD Using a Model-Informed Approach**

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**Background:** A number of clinical studies and meta-analyses have been published to compare the efficacy of psychostimulants for the treatment of ADHD. However, the comparative efficacy of long-acting amphetamine versus methylphenidate products based on the exposure-response relationship have not been fully addresses. The objective of this study was to develop a model-informed approach for comparing the exposure-efficacy relationship of lisdexamfetamine dimesylate (LDX, a long-acting d-amphetamine prodrug) and osmotic-release oral system methylphenidate (OROS-MPH) in adolescents with ADHD.

**Methods:** The efficacy data (change in ADHD-RS-IV total score from baseline) were extracted from a publication (CNS Drugs (2017) 31:999–1014) reporting the results of a randomized, double-blind, multicenter, parallel-group, active-controlled, forced-dose titration, safety and efficacy study of LDX compared with MPH with a placebo reference arm, in adolescents aged 13-17 years with ADHD. This was a 6-week study with forced titration, 4 weeks; dose maintenance, 2 weeks, and a 1-week follow-up period. The PK of MPH was characterized using a convolution-based model with time-varying absorption (Clin Pharmacol Ther. 2017 Dec;102(6):951-960). The PK of d-amphetamine was characterized by a one compartment model (Clin Drug Investig (2016) 36:341–356). The average PK concentrations and the average changes of ADHD-RS-IV from baseline estimated on days 6,13,20,27,34, and 41 were used in the analysis. The longitudinal decrease of the change from baseline of the ADHD-RS-IV scores in the placebo arm was described by a bounded exponential function:  $\text{Placebo} = \text{Bas} * \text{EXP}(-\text{Time}/\text{Rate}) + \text{Lbound}$ . A preliminary analysis indicated that the drug concentrations measured in plasma were not directly related to efficacy. Therefore, drug concentrations in the effect compartment ( $C_e$ ) were estimated and used in the exposure-



response model (CPT Pharmacometrics Syst Pharmacol. 2014 Jan 2;3:e88). The pharmacodynamic effect was described by a Ce related drop from placebo response. The observed ADHD-RS-IV scores in the active arms were modeled as:  $\text{Effect} = \text{Placebo} * (1 - \text{Emax} * \text{Ce} / (\text{EC50} + \text{Ce}))$ . Where, EC50 is the Ce values associated with half of the theoretical maximal response (Emax).

**Results:** The estimated average plasma concentrations on the last day of the maintenance period were ~7 and ~53 (ng/mL) and the associated concentrations at the effect site were 1.5 and 0.33 (ng/mL) for MPH and LDX, respectively. The analysis indicated that the efficacy can be improved by increasing the exposure of LDX and MPH. The exposure-response model indicated that MPH was ~40% more potent than LDX based on the EC50 values (1.14 and 1.63 (ng/mL), respectively). However, the estimated treatment related maximal improvement with respect to placebo (Emax) was ~4 time larger for LDX with respect to MPH (0.426 and 1.94, respectively). These results indicated that the response to MPH at the maximal dose of 72 mg/day is closed to the maximal attainable response while the response to LDX (70 mg/day) is numerically superior to the response to MPH and that this response can be increased by increasing the exposure.

**Conclusions:** The exposure-response model provided a good description of the effect of LDX and MPH on the trajectory of ADHD-RS-IV scores in Adolescents with ADHD.

Lisdexamfetamine showed better performances than OROS MPH in adolescents with ADHD in the forced-dose study, as measured by ADHD-RS-IV scores.

## **S6. RATIONALE AND DESIGN OF THREE PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES TO EVALUATE THE EFFICACY AND SAFETY OF SPN-810 (EXTENDED-RELEASE MOLINDONE) FOR THE TREATMENT OF IMPULSIVE AGGRESSION IN YOUTHS WITH ADHD**

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**Background:** Impulsive aggression (IA) is a maladaptive form of aggression that is reactive, overt, and occurs outside of the acceptable social context. IA is often secondary to attention-deficit/hyperactivity disorder (ADHD) and persists despite the primary ADHD therapy. In a post-hoc analysis of the Multimodal Treatment study of children with ADHD, 26% of children 6-9.9 years old whose ADHD symptoms are treated by medication exhibited untreated aggressive behavior. When aggression persists, a different class of medication is often added to specifically treat aggressive behavior, although no FDA-approved medication is currently available. Because IA is a serious clinical concern amplifying the risk of poor outcomes in those with ADHD, treatment of IA in youths with ADHD is needed. This poses a significant challenge in clinical practice, as few evidence-based treatments are available. SPN-810 is currently in Phase 3 studies for treatment of IA associated with ADHD in subjects 6-17 years old.

**Methods:** The SPN-810 Phase 3 program consists of three efficacy studies and one open-label safety study. In two of the ongoing efficacy studies (P301 and P302), 36 mg/day SPN-810 is compared with placebo in subjects 6-12 years old. In the recently initiated Phase 3 efficacy study (P503), a flexible-dose of SPN-810 (starting at 36 mg/day, up to 54 mg/day) will be tested and compared to placebo in subjects 12-17 years old. The open-label, long-term safety study (P304) is still ongoing. The treatment phase in the efficacy studies includes a 2-week titration period and a 3-week maintenance period. The primary efficacy outcome is the percent

change in frequency of IA behaviors in the treatment period relative to baseline, as measured by a newly developed electronic observer-reported outcome (eObsRO) tool. The secondary efficacy outcomes include: investigator-rated Clinical Global Impression (CGI)-Improvement (CGI-I); caregiver-rated CGI-I; investigator-rated CGI-Severity (CGI-S); caregiver-rated CGI-S (P503 only); Child Health Questionnaire Parent Form 28-item; Swanson, Nolan and Pelham Rating Scale – Revised; Retrospective-Modified Overt Aggression Scale (R-MOAS) (P503 only); R-MOAS remission rate (P503 only); Parenting Stress Index-Short Form (P301 and P302 only); and the Stress Index for Parents of Adolescents (P503 only). Safety assessments include monitoring/reporting of adverse events, evaluation of extrapyramidal symptom scales, clinical laboratory tests, ECGs, vital signs, the Columbia-Suicide Severity Rating Scale, and the Infrequent Behaviors Checklist. After completing the 3-week maintenance period, subjects have the option to enter the open-label extension (OLE; P304).

**Results:** The Phase 3 enrollment update, available as of August 7, 2018, is about 91% for study P301 and about 77% for study P302. Enrollment in the OLE is about 90%. Study P503 was initiated in July 2018.

**Conclusions:** There is an unmet need for a medication to treat IA in children with ADHD. Based on demonstrated efficacy and safety in two Phase 2 studies, SPN-810 is being investigated in Phase 3 studies as an adjunctive treatment for IA in youths aged 6-17 years with IA behaviors in spite of a stable dose of standard ADHD treatment.

## **\*\*S7. HUMAN ABUSE POTENTIAL OF INTRANASAL SERDEXMETHYLPHENIDATE (SDX), A NOVEL PRODRUG OF D-METHYLPHENIDATE, IN RECREATIONAL STIMULANT ABUSERS**

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**Background:** Serdexmethylphenidate (SDX) is a prodrug of d-methylphenidate (d-MPH) currently being developed as the major active pharmaceutical ingredient (API) in KP415, an investigational product for the treatment of ADHD. SDX as the intact prodrug produces no discernible pharmacodynamic effects and is gradually converted to the active moiety, d-methylphenidate, when administered orally. Nonmedical use of prescription stimulants, by oral and non-oral routes, has been widely reported in adolescents and adults, with ~40% of past-month nonmedical users reporting intranasal (IN) administration. It is therefore important to evaluate novel stimulant-like drugs for their abuse potential by all relevant routes of abuse. The objective of this study was to evaluate the human abuse potential of IN SDX in recreational stimulant abusers.

**Methods:** This was a Phase 1, randomized, double-blind study to compare the human abuse potential and pharmacokinetics (PK) of IN SDX and IN d-MPH HCl in recreational stimulant users with nasal insufflation experience. Subjects (n=45 completers) who were able to discriminate IN d-MPH HCl (40 mg) from placebo entered the Treatment Phase, consisting of a 3-treatment, 3-period, crossover design in which subjects received single IN doses of SDX (80 mg), d-MPH HCl (40 mg mixed with 40 mg microcrystalline cellulose [MCC]), and matching placebo powder (80 mg MCC). The doses of SDX and d-MPH HCl are equivalent with respect to molar amount of d-MPH. Blood samples and abuse potential measures were collected at different times after dosing, and safety assessments were conducted. The primary endpoint was maximum effect (Emax) for Drug Liking, assessed on a 0-100 point, bipolar, visual analog scale. Analyses of the primary endpoint were conducted as superiority- and non-

inferiority-type hypotheses with appropriate margins for each pairwise comparison, whereas secondary endpoints were conducted as confirmatory-type hypotheses with no margins.

**Results:** Following IN SDX, peak (C<sub>max</sub>) and overall (AUC<sub>inf</sub>) d-MPH exposure were approximately 13.2% and 24.3% of the exposure observed with IN d-MPH HCl. Mean Drug Liking E<sub>max</sub> scores were significantly lower following IN SDX compared to IN d-MPH HCl (71 vs. 93, p<0.0001 with margin=10). Confirming the overall study validity, mean Drug Liking E<sub>max</sub> scores were significantly higher for IN d-MPH HCl vs. IN placebo (93 vs. 51, p<0.0001 with margin=15); however, IN SDX was not similar to IN placebo (71 vs. 51, p=0.99 with margin=11). For Take Drug Again, a secondary endpoint, mean E<sub>max</sub> scores for SDX were significantly lower compared to IN d-MPH HCl (60 vs. 80, p=0.0021), and significantly higher compared to IN placebo (60 vs. 49, p=0.0091), a profile that was also observed for other secondary endpoints, including Overall Drug Liking and Feeling High. Typical stimulant-associated adverse events (AEs) such as euphoric mood and palpitations were more common following IN d-MPH HCl, whereas nasal-related AEs such as nasal discomfort and nasal congestion were more common following IN SDX.

**Conclusions:** In subjects with a history of intranasal stimulant use, IN SDX produced pharmacodynamic effects that were significantly lower than with IN d-MPH HCl on multiple abuse-related endpoints, and produced lower exposure to d-MPH, indicating that SDX is not efficiently converted to d-MPH when snorted. The performance of SDX under these conditions suggests that it would be unlikely to reinforce IN drug-taking behavior in a manner similar to that for IN d-MPH HCl.

## **S8. HUMAN ABUSE POTENTIAL OF ORAL SERDEXMETHYLPHENIDATE (SDX), A NOVEL PRODRUG OF D-METHYLPHENIDATE, COMPARED TO FOCALIN®XR AND PHENTERMINE IN RECREATIONAL STIMULANT ABUSERS**

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**Background:** Serdexmethylphenidate (SDX) is a novel prodrug of d-methylphenidate (d-MPH) that has negligible binding (K<sub>i</sub> >10 uM) at monoamine transporters or other targets associated with abuse potential. Thus, SDX does not produce any apparent pharmacodynamic effects until it is converted to d-MPH, a process which occurs efficiently after oral but not intranasal or intravenous administration. SDX is under development as the major active pharmaceutical ingredient (API) in KP415, an investigational product for the treatment of ADHD. SDX is a new chemical entity and is currently unscheduled under the Controlled Substances Act. The objective of this study was to examine the human abuse potential of suprathreshold oral doses of SDX compared to Focalin XR (Schedule II stimulant) and phentermine (Schedule IV stimulant) in recreational stimulant users.

**Methods:** This was a Phase 1, randomized, double-blind, single-dose, active- and placebo-controlled study in recreational stimulant users. Following Screening, subjects (n=45 completers) who were able to discriminate double-blind Focalin XR (80 mg) from placebo entered the Treatment Phase, consisting of a 5-treatment, 5-period, 10-sequence, crossover design in which subjects received single oral doses of SDX (120 and 240 mg), Focalin XR (80 mg), phentermine (60 mg), and placebo. Pharmacodynamic assessments included “at-the-moment” measures (e.g., Drug Liking, Good Effects, Bad Effects) taken from 15 minutes to 24 hours post-dose and retrospective measures (e.g., Take Drug Again, Overall Drug Liking) taken 12 and 24 hours post-dose. The primary endpoint was maximum effect (E<sub>max</sub>) for Drug Liking, assessed on a 0-100 point, bipolar, visual analog scale (VAS). Analyses of the primary endpoint were conducted as superiority- and noninferiority-type hypotheses with appropriate

margins, whereas secondary and exploratory endpoints were conducted as confirmatory-type hypotheses with no margins.

**Results:** Drug Liking Emax scores for 80 mg Focalin XR were significantly higher than for placebo (mean = 82 vs. 56,  $p < 0.0001$  with margin=15), confirming study validity. Mean Drug Liking scores for both doses of SDX increased gradually after administration and never exceed 60 on the VAS. Drug Liking Emax scores for 120 and 240 mg SDX were significantly lower than that for 80 mg Focalin XR (63 vs. 82,  $p = 0.0011$ ; and 64 vs. 82,  $p = 0.0058$ , both comparisons with margin=10), yet not non-inferior to placebo (63 vs 56,  $p = 0.0567$ ; and 64 vs.56,  $p = 0.1502$ , both comparisons with margin=11). When SDX was compared to phentermine, Drug Liking Emax for the 120 mg SDX dose was significantly lower (63 vs. 80,  $p = 0.0195$  with margin=10), while the 240 mg SDX dose was not significantly different (64 vs. 80,  $p = 0.0664$  with margin=10). Analyses of other “at-the-moment” pharmacodynamic endpoints showed the same pattern of differences with both active controls, such that the general rank order of abuse-related effects was Focalin XR  $\geq$  phentermine  $>$  SDX 240 mg  $\approx$  SDX 120 mg  $>$  placebo. For retrospective endpoints of Take Drug Again and Overall Drug Liking, this rank order was phentermine  $\geq$  Focalin XR  $>$  SDX 240 mg  $\approx$  SDX 120 mg  $\geq$  placebo.

**Conclusions:** SDX produced a gradual onset of abuse-related effects and maximal effects were generally lower than a Schedule II and Schedule IV stimulant. These data are consistent with prior reports demonstrating that rate of onset is a critical determinant of the abuse potential of stimulants, and indicate that SDX may have lower oral abuse potential than currently available stimulant products.

## **S9. OPEN-LABEL DOSE-OPTIMIZATION OF AN AMPHETAMINE EXTENDED-RELEASE ORAL SUSPENSION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER**

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**Background:** Report the efficacy of open-label amphetamine extended-release oral suspension (AMPH EROS) for the treatment of children with attention-deficit/hyperactivity disorder (ADHD).

AMPH EROS has a 1-hour onset of effect and a duration of action of 13 hours and was approved by FDA for treatment of ADHD in children aged 6-17 years based on a double-blind, placebo-controlled efficacy and safety study in children aged 6-12 years with ADHD. A significant treatment difference in change from pre-dose SKAMP-combined score was observed at the primary endpoint of 4 hours post-dose ( $p < 0.0001$ ) and each post-dose time point assessed (1, 2, 4, 6, 8, 10, 12, 13 hours).

Data reported here are from the 5-week, open-label dose optimization period. These efficacy data support the primary endpoint result.

**Methods:** Males and females aged 6 to 12 years with ADHD enrolled and began open-label treatment with 2.5 mg or 5 mg/day of AMPH EROS titrated in 2.5-10 mg/day increments until optimal dose (maximum 20 mg/day). Doses could be decreased for tolerability. Subjects took morning AMPH EROS for 5 weeks. Other efficacy outcomes during the open-label dose optimization phase: ADHD-RS (ADHD-Rating Scale), CGI-S (Clinical Global Impression of Severity), CGI-I (CGI-of Improvement) and CPRS (Conners' Parent Rating Scale). All subjects were assessed for safety.

**Results:** For the ITT population (n=99): treatment with AMPH EROS was associated with a mean change in ADHD-RS-IV (baseline to end of the open-label dose optimization; week 6) of 28.2 ( $\pm 9.03$ ) (Baseline score = 41.3  $\pm 7.95$ ). 90.9% of subjects had a change from baseline to open-label week 6 of  $\geq 50\%$  in the ADHD-RS-IV total score and were defined as responders. The CGI-S scores decreased continuously from baseline, with a high 4.8 at baseline to a low of 2.0 at open-label week 6. The percentage of subjects classified as moderately ill or greater correspondingly decreased from 97% at Baseline to 1% at open-label week 6. The decrease in the CGI-I over the study was similar to the change in CGI-S scores. CPRS for most categories decreased continuously from Baseline to open-label week 6. Mean change from baseline to open-label week 6 on the CPRS inattention T-score subscale was -25.3 ( $\pm 14.38$ ) and -24.4 ( $\pm 13.87$ ).

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 in this open-label dose optimization. The AE profile of AMPH EROS was consistent with those of other amphetamine products.

## **\*\*S10. TREATING CLINICAL AND SUB-CLINICAL SYMPTOMS OF ADHD WITH PCSO-524, A NOVEL MARINE OIL EXTRACT**

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<sup>1</sup>Monash University

**Background:** Children with attention-deficit/hyperactivity disorder (ADHD) tend to perform worse academically than their age-matched peers. Despite increased interest in the treatment of ADHD and its associated symptoms, no definitive explanation for its aetiology currently exists. Associated symptoms have been linked to dietary deficiencies, including low levels of the polyunsaturated fatty acid omega-3. This study investigated the effects of an omega-3 marine oil extract (PCSO-524®) on inattention, hyperactivity, cognition and electrophysiological changes in children and adolescents.

**Methods:** PCSO-524® or a matched placebo was administered for 14 weeks to 144 participants (123 males/21 females; mean age 8.7 years). The primary outcome was the Conners' Parent Rating Scale assessing parental reports of behavioral problems. Secondary outcomes assessed changes in cognition and mood. Brain electrical activity was recorded from 60 sites on the scalp positioned according to the extended 10-10 system using an electrode cap.

**Results:** No significant improvements were noted on the primary outcome. Repeated measures ANOVA on post hoc sub-sample analysis indicated significant improvements in hyperactivity ( $p = 0.04$ ), attention ( $p = 0.02$ ), learning ( $p = 0.05$ ) and probability of ADHD ( $p = 0.04$ ) with a medium to large average effect size ( $d = 0.65$ ). Significant cognitive improvements in a whole sample repeated measures ANCOVA were noted on recognition memory between baseline and week 8 over placebo ( $p = 0.02$ ). EEG analysis revealed significant decreases in eyes-open absolute alpha in favor of PCSO-524® ( $p < 0.05$ ) across multiple regions.

**Conclusions:** The current research indicates that the natural marine oil supplement PCSO-524® may have a role in improving symptoms of attention and behavior, as well as reducing theta and alpha brain wave disparities in children and adolescents experiencing clinical and sub-clinical levels of ADHD symptoms.

## **S11. AN INNOVATIVE SMS INTERVENTION TO IMPROVE ADHERENCE TO STIMULANTS IN CHILDREN WITH ADHD**

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**Background:** ADHD is a prevalent neurobiological disorder associated with a wide range of adverse outcomes. Large datasets document that stimulants decrease the risk for many adverse outcomes, yet compliance with stimulants remains poor. This study examined the effectiveness of a novel text messaging intervention aimed to improve the poor rate of adherence to stimulant medications in children with ADHD.

**Methods:** Subjects were children ages 6-12, who were prescribed a stimulant medication by their primary care physician for ADHD treatment. For comparators, we identified at a 10-1 ratio (age and sex matched) pediatric patients from the Partners HealthCare electronic medical record, who had been prescribed stimulant medications over a 2-year period. Timely prescription refills were determined using prescriptions documented in the electronic medical record.

**Results:** Results showed that 51% of patients receiving treatment as usual refilled their prescriptions in a timely fashion promptly enough to be considered consistently medicated. In contrast, 91% of the SMS intervention group refilled their prescriptions in a timely manner.

**Conclusions:** These data indicate that a novel ADHD-centric text messaging intervention significantly improved patient engagement to treatment with stimulants in children with ADHD. Findings provide strong support for the utility of this readily accessible, inexpensive and widely available technology to improve the poor rate of adherence to stimulant treatment in children with ADHD. To the best of our knowledge, this study is the first digital health intervention aimed at improving adherence to stimulant medication for children with ADHD.

## **S12. PROBLEMS WITH EMOTIONAL CONTROL IN CHILDREN WITH ADHD PREDICTS CO-OCCURRING INTERNALIZING PROBLEMS IN GIRLS AND EXTERNALIZING PROBLEMS IN GIRLS AND BOYS IN ADOLESCENCE**

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**Background:** Children diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) are susceptible to experiencing negative functional outcomes later on in life, including the emergence of comorbid psychopathology (e.g., anxiety, depression, substance use) in adolescence in adulthood. Symptoms of these comorbid disorders tend to either transpire or worsen during adolescence. Therefore, it is essential that we examine whether or not there are factors that we can account for in childhood that would be predictive of these often co-occurring disorders. Additionally, studies have shown that sex may be a key moderator of functional outcomes within the ADHD population. This study aims to inform clinical work by identifying behavioral predictors of internalizing and externalizing problems in adolescence among girls and boys with ADHD without comorbid internalizing disorders in childhood.

**Methods:** Parent-reported questionnaire data was acquired on 62 children with ADHD (42 males and 20 females) at two different time points. At the first time point, the participants' age range was 8-12 years and only comorbid oppositional defiant disorder (ODD) was permitted.

The second time point occurred at least two years after their first time point in the 12-17 year age range and all comorbidities were permitted. Analyses focused on parent-report questionnaire data at each time point. We examined correlations between problems with emotional control at time 1 (Emotional Control T-score from the Behavior Rating Inventory of Executive Function, Second Edition) and problems with anxiety (Anxiety Problems T-score from the Behavior Assessment System for Children, Second Edition), or oppositional behavior (ODD T-score from the Conners' 3rd Edition) at time 2 in the full sample of children with ADHD. Next, we conducted regression analyses to test whether sex moderated the relationship between problems with emotional control at time 1 and anxiety or ODD at time 2 using the PROCESS macro in SPSS. We included age at time 1 and difference in age from time 1 to time 2 as covariates in the regressions.

**Results:** Correlation results in the full sample of children with ADHD indicated that childhood emotional control was associated with adolescent oppositional behavior ( $r=.359$ ,  $p<.001$ ) and marginally associated with adolescent anxiety ( $r=.235$ ,  $p=.066$ ). Sex was shown to moderate the relationship between childhood emotional control and adolescent anxiety (coeff=-.68,  $t=-2.67$ ,  $p=.010$ ), such that a strong positive relationship was observed among girls ( $p=.003$ ) but not among boys ( $p=.965$ ). In contrast, sex did not moderate the relationship between childhood emotional control and adolescent oppositional behavior (coeff=-.21,  $t=-.80$ ,  $p=.425$ ), although emotional control was a significant predictor of oppositional behavior in this model (coeff=.47,  $t=2.10$ ,  $p=.041$ ).

**Conclusions:** The results of this study suggest that, among individuals with ADHD, problems with emotional control in childhood can predict adolescent co-occurring internalizing problems (anxiety) in girls and externalizing problems (ODD) in both girls and boys. Utilizing this information for clinical practice is critical in understanding how ADHD as a disorder progresses as children enter adolescence and how that informs treatment. Future studies should focus on examining other possible predictive factors of comorbid disorders as children with ADHD transition into adolescence and are at greater risk for the emergence of comorbid psychopathology.

### S13. MIND WANDERING IN ADHD, A LITERATURE REVIEW

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**Background:** Mind wandering is an emergent construct in cognitive neuroscience. Mind wandering is generally understood as unintended shifting of attention from a task at hand toward internal thoughts. While some agree that mind wandering is often a detrimental process, there is much debate as to its purpose and origin. Researchers of mind wandering found associations with impulsivity, impairments in sustained attention, and hyperactivity (i.e., fidgeting), which are features that overlap with symptoms of attention deficit/hyperactivity disorder (ADHD). It is reasonable to hypothesize that mind wandering may be a common concomitant of ADHD; however, how best to define mind wandering in ADHD, and whether specific symptoms of ADHD may be quantifiable proxies for mind wandering remains unclear. Individuals with ADHD and mind wandering may have unique neurobiological profiles and portend different responses to treatments and variable outcomes. Incorporating mind wandering into clinical evaluation may help individualize care for individuals with ADHD. We sought to conduct a systematic review of journal articles pertaining to of mind wandering and ADHD to evaluate what is known about the co-occurrence of mind-wandering in individuals with ADHD.

**Methods:** We conducted a search of the scientific literature on mind wandering in ADHD using PubMed and PsycINFO/OVID databases.

**Results:** Our search identified 24 PubMed articles and 23 PsycINFO/OVID, of which 23 were duplicates. Two additional articles were identified as relevant from cross reference review of the previous articles. From the 26 identified articles, only nine met our a priori inclusion and exclusion criteria. We excluded four articles that did not pertain to individuals with ADHD, three did not operationalize mind wandering, three did not relate to mind wandering in ADHD, and five were theoretical (not primary research) about mind wandering.

**Conclusions:** The present review revealed that there is a paucity of research on mind wandering in ADHD. Our search found only one article in a pediatric population, suggesting even less is known about mind wandering in children with ADHD. The work that has been done indicates a co-morbidity of the phenomenon of mind wandering in people affected by ADHD and that it confers greater functional impairment. The specific ADHD symptoms correlate with mind wandering is unclear and warrants more research. Further investigation into clinical trajectories and outcomes for individuals with concomitant mind wandering and ADHD could provide information on the implications of this comorbidity and could prompt changes in treatment. In addition, neuroimaging studies could reveal neurobiological underpinnings of mind wandering in ADHD and could guide treatment development.

#### **S14. SENSITIVITY TO REWARD PREDICTS IMPROVEMENT IN INHIBITORY CONTROL WITH REWARD AMONG COLLEGE STUDENTS WITH ADHD AND ALCOHOL-RELATED PROBLEMS**

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**Background:** Attention-Deficit Hyperactivity Disorder (ADHD) and elevated substance use are associated with impaired inhibitory control and atypical response to reward. Consistent with etiological models of ADHD postulating an interaction of cognitive and motivational deficits, reward has been shown to improve inhibitory control in individuals with ADHD. Individual differences in sensitivity to reward (SR), a neurobiologically based motivational trait, relates to improvement in inhibitory control with reward among children with ADHD. The current study examined whether self-reported SR among college students with ADHD and co-occurring alcohol-related problems predicts within-session improvement in inhibitory control with performance-based rewards.

**Methods:** Participants include college students (ages 18-22) with DSM-5 & ADHD and elevated alcohol use (i.e., AUDIT >7) (n=34) enrolled in a treatment study to reduce problem-drinking behaviors. Participants completed the Sensitivity to Punishment & Sensitivity to Reward Questionnaire (SPSRQ), a self-report measure of SR, and a motivational stop signal task (mSST), a neurocognitive measure of inhibitory control. The mSST includes two reward blocks in which participants earned money for correct responses and two no-reward blocks during which money could not be earned or lost. Inhibitory control was measured by stop signal reaction time (SSRT) averaged across blocks within reward condition, with higher values indicating worse inhibitory control. Improvement in inhibitory control with reward was based on the difference in SSRT from the no-reward to reward blocks such that higher values represent greater improvement in inhibitory control with reward. Correlations between SR, no-reward SSRT, and improvement in SSRT with reward were examined. Linear multiple



regression was conducted to determine if self-reported SR predicted improvement in inhibitory control with reward after accounting for ADHD symptom severity (BAARS total score). All analyses focused on relationships among baseline measures obtained prior to the initiation of treatment. Participants taking stimulant medication did not take their medication within 24 hours of testing. Other psychotropic medications were permitted.

**Results:** Higher self-reported SR correlated with worse inhibitory control without reward ( $r=.559$ ,  $p=.001$ ) and greater improvement in SSRT with reward ( $r=.448$ ,  $p=.008$ ). Furthermore, the regression with self-reported SR and ADHD symptoms predicting improvement in SSRT with reward was significant,  $R^2=.21$ ,  $F(2, 31)=4.3$ ,  $p=.025$ , with SR as a significant predictor ( $\beta=6.98$ ,  $p=.015$ ) whereas ADHD symptom severity was not related to change in SSRT with reward ( $\beta=0.78$ ,  $p=.506$ ). Furthermore, when controlling for medication use and depressive symptoms, SR remains a significant predictor of change in SSRT with reward ( $\beta=0.620$ ,  $p=.004$ ).

**Conclusions:** Higher SR predicts greater improvement in inhibitory control with reward among college students with ADHD and co-occurring alcohol-related problems after accounting for ADHD symptom-severity, medication use, and depressive symptoms. These results suggest that individual differences in sensitivity to reward are important to consider when examining whether reward improves inhibitory control in adults with ADHD.

## **S15. IMPAIRED GOAL-DIRECTED BEHAVIOR IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER**

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**Background:** Aside from its clinical symptoms of inattention, impulsivity, and hyperactivity, patients with attention/deficit-hyperactivity disorder (ADHD) exhibit motivational and cognitive impairments that affect their daily life functioning. These impairments may reflect a deficit in action control, that is, an inability to flexibly adapt behavior to changing consequences. The two main systems that modulate action control are the goal-directed system, forming action-outcome associations, and the habitual system, acquiring stimulus-response associations. We previously showed that spontaneously hypertensive rats (SHR), an inbred rodent model of ADHD, show impairments in goal-directed action control, and instead relied predominately on the habitual system. Further, we showed that outcome-sensitive goal-directed behavior was restored in SHR rats following injections of methylphenidate, dopamine D2 receptor agonist or dopamine D1 receptor antagonist. In this study, we examined action control patterns in children with ADHD using the same outcome-devaluation paradigm to distinguish between goal-directed and habitual behaviors. Our central hypothesis is that patients with ADHD have a deficit in goal-directed behavior and a dominant habitual response similar to SHR rats.

**Methods:** We tested 19 off-medication children with ADHD and 21 healthy controls. Participants were 6-10 years old and were group matched for age and sex. We tested patterns of action control using a computer-based task of the outcome devaluation paradigm that consists of three phases; a training phase, a devaluation phase and a choice test.

**Results:** Healthy subjects and children with ADHD were successful at acquiring action-outcome associations, demonstrating intact instrumental response. However, patients with

ADHD failed to employ the goal-directed system to control their actions. Instead, they demonstrated a predominance of habitual behavior.

**Conclusions:** In line with our previous findings in SHR, our results indicate that children with ADHD show a behavioral deficit in controlling their actions using goal-directed behavior and compensated for that by relying on the reflective, habitual behavior. This is the first study to show a deficit in action control in patients with ADHD. Unraveling this deficit can broaden our understanding of the motivational impairments, inflexible actions and the fundamental behavioral symptoms observed in ADHD.

## **S16. BUILDING PEER RELATIONSHIPS IN ADHD USING THE SUMMER TREATMENT PROGRAM**

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**Background:** The development of peer relationships is an area of challenge for children with Attention-Deficit/Hyperactivity Disorder (ADHD). These challenges arise early in childhood and persist into adolescence. The Summer Treatment Program (STP) represents a model day-treatment program for children with ADHD, incorporating behavioral and social skills training, along with sports training and supported practice engaging in group activities. Improving children's social functioning is an explicit goal of the program, but there is limited direct evidence for the program's effectiveness in building peer relationships and fostering friendships.

**Methods:** The STP was conducted by the UW Autism Center in collaboration with Seattle Children's. The 5-week program was conducted Monday through Friday 9:00am to 3:00p and included a token economy, social skills training, and sports instruction. Rigorous training and fidelity procedures were in place to ensure manualized implementation. Children were divided into groups of 14, with 6 graduate or undergraduate student counselors assigned to each group. The staff of 63 included 5 doctoral level psychologists and 6 master's level clinicians. Out of 124 children ages 5-12 enrolled during the summer 2018, 45 had a primary diagnosis of ADHD and were included in this analysis. Following procedures described by Cairns and Cairns (1994), children were asked weekly to compile a "Buddies List" comprised of children they "like to hang out with". A reciprocal friendship was defined as two children nominating each other in the same week. We hypothesized that children would build new friendships during the first two weeks of the program, and that the number of friendships would be maintained during the remainder of the program.

**Results:** A 2-slope model of individual change in reciprocal friendships was fit using a linear mixed effects model (using R package: nlme). The 2 slope parameters allowed us to measure the change in the number of reciprocal friendships from Weeks 1 to Week 3 (slope 1) and also from Week 3 to Week 5 (slope 2). The intercept was placed at Week 3, the inflection point between these two periods. The slope 1 parameter was highly significant finding that on average children gained in reciprocal friendships by a rate of .67 per week from Week 1 to Week 3 ( $b = 0.67$ ,  $SE = 0.11$ ),  $t(157) = 5.92$ ,  $p < .0001$ ), with no significant change in reciprocal friendships for the slope 2 parameter, Week 3 to Week 5 ( $b = -0.06$ ,  $SE = 0.12$ ,  $t(157) = -0.51$ ,  $p = 0.61$ ). The final two-slope model yielded the following equation for reciprocal friendships:  $1.25 + (.67 * \text{Week 1 to Week 3}) + (-0.06 * \text{Week 3 to Week 5})$ .

**Conclusions:** Previous research into the STP has indicated behavioral gains for children with ADHD, as well as increases in observable pro-social behavior. However, this is the first study

to our knowledge to assess reciprocal friendships directly from the participating children over the course of the STP. We found that children with ADHD developed reciprocal friendships over the first 3 weeks of the STP, and that the number of relationships was maintained for the remainder of the program. This suggests that the STP may support children with ADHD in building reciprocal friendships, a central developmental milestone of middle childhood that is associated with increased well-being, greater academic achievement, and reduced challenging behaviors.

## **S17. EVENINGNESS DIURNAL PREFERENCE AND CANNABIS USE AMONG ADULTS SEEKING AN ADHD EVALUATION**

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<sup>1</sup>Duke University Medical Center

**Background:** Adults with ADHD are at risk for problematic cannabis use, and recent research has focused on understanding the mechanisms contributing to this elevated risk. Our recent work has shown that one motivation for cannabis use among adults with ADHD is the perception that cannabis is therapeutic for ADHD. A related, but yet unexamined, possibility is that cannabis may be used by adults with ADHD to treat sleep problems common to this population. Specifically, adults with ADHD tend to have a greater preference for eveningness, which can translate into difficulties falling asleep at appropriate times. Eveningness has also been shown to be associated with cannabis addiction, and among psychiatric populations more broadly, difficulties falling asleep have been cited as a motivation for cannabis use. The aim of this study was to assess associations between recent cannabis use and diurnal preference (i.e., morningness/eveningness) among outpatients seeking evaluation of ADHD. We also explored the relationship between eveningness preference and early onset of cannabis use.

**Methods:** Fifty-two adults (age  $M = 40$ ,  $SD = 13$ ; 60% male) seeking an evaluation for ADHD through an outpatient clinic at a university medical center participated. Diurnal preference was assessed using the 13-item Composite Morningness Scale (CMS) and past/current cannabis use was assessed via the Conners' Adult ADHD Diagnostic Interview for DSM (CAADID) Part I. ADHD severity was determined by the Conners' Adult ADHD Rating Scale (CAARS). Recent cannabis use (i.e., use within the past 5 years) and early cannabis use status (i.e., use by age 15) were considered. Regressions covarying for ADHD symptom severity assessed group differences between 1) recent and non-recent cannabis users and 2) early cannabis users (onset < age 15) and late cannabis users (onset > age 15).

**Results:** Fourteen of 52 individuals endorsed recent cannabis use. Recent users showed greater preference toward eveningness ( $M = 28.57$ ,  $SD = 8.02$ ) than individuals who were non-recent users ( $M = 35.00$ ,  $SD = 9.75$ ) after covarying for ADHD symptom severity ( $F(2, 45) = 4.92$ ,  $p = .03$ ). When early cannabis use was considered, six participants met our definition of early user. After controlling for ADHD symptom severity, individuals endorsing early cannabis use displayed greater preference toward eveningness ( $M = 24.50$ ,  $SD = 5.36$ ) than individuals endorsing later onset of cannabis use ( $M = 33.88$ ,  $SD = 9.51$ ) ( $F(2, 19) = 4.48$ ,  $p < .05$ ).

**Conclusions:** Findings from this preliminary study suggest that among adults seeking an ADHD evaluation, individuals endorsing recent cannabis use display a greater preference for eveningness than those without recent use. In addition, individuals who began using cannabis earlier in development were also more likely to report greater preference for eveningness currently. Future research should examine the direction of effects between diurnal preference, cannabis use, and ADHD. In addition, future studies should evaluate the timing of cannabis use among adults with ADHD and determine whether sleep problems, including eveningness preference, motivate cannabis use in this population.

## **S18. STIMULANT-INDUCED PSYCHOSIS - HOW DOES IT PRESENT IN CLINIC AND WHAT ARE THE RISK FACTORS? TWO CASE REPORTS AND A LITERATURE REVIEW**

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**Background:** Attentional symptoms in the collegiate and post-graduate population can lead patients to seek ADHD treatment for the first time as adults. But these symptoms may also herald the onset of psychosis. Work attempting to elucidate the relationship between childhood ADHD, stimulant exposure and the later onset of psychosis has shown a decreased age of onset of psychosis in those exposed to stimulants as children and increased hazard ratio of at least 4 for the later development of a psychotic disorder in those diagnosed with ADHD. However, there is a relative dearth of work on the phenomenon in those diagnosed with ADHD and treated with stimulants for the first time as adults.

**Methods:** A comprehensive literature review and case series of psychosis in the setting of adult diagnosis of ADHD and subsequent amphetamine treatment is utilized to further elucidate this relationship and attempt to identify risk factors for predicting the onset of psychosis.

**Results:** There appears to be a dichotomous relationship between adult diagnosis and stimulant treatment of ADHD and the onset of psychosis. Inappropriate over-exposure (or increased exposure due to drug interactions) is capable of triggering a time-limited substance-induced psychosis. Conversely, prodromic psychosis presenting as attentional struggles in collegiate and graduate education may also lead to this diagnosis and treatment. Presently, it is unclear whether exposure to stimulants in the second group can hasten, unmask or induce a chronic psychotic syndrome which otherwise may have remained prodromic or dormant.

**Conclusions:** It is clear that over-exposure to stimulants can induce a time-limited psychosis. Likewise, it is clear that exposure to stimulants in those at risk may interact negatively with the onset of psychotic illness. However, understanding this relationship and the relative risk in patients diagnosed with ADHD for the first time as adults will require further work. Importantly, epidemiological study of the risk at the population level will be helpful in determining whether progression to chronic psychosis is common enough to warrant undertaking a prospective, randomized, controlled trial of stimulant vs. non-stimulant treatment in a carefully selected population of patients with adult-onset ADHD.

## **S19. THE PREDICTIVE UTILITY OF RETROSPECTIVE SELF-REPORT OF EARLY TEMPERAMENT FOR ADHD DIAGNOSTIC STATUS IN ADULTHOOD**

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**Background:** ADHD is a chronic developmental disorder with several known etiological factors (e.g., genetic, environmental). However, a growing literature has suggested that temperament may also play a role in the development of ADHD. For example, early temperamental characteristics have been shown to be related to the diagnosis of ADHD later in childhood. Moreover, adults with ADHD are more likely to exhibit specific personality features. Despite previous research finding predictive utility of early temperament on the development of other psychiatric disorders in adulthood, no studies to date have investigated this predictive relationship in ADHD. The current study addresses this gap by examining

retrospective self-report ratings of early temperament and investigating whether they predict ADHD and comorbid diagnoses in an adult outpatient sample seeking an ADHD assessment.

**Methods:** Adult participants (n = 654) were recruited from an outpatient psychiatry clinic at a university medical center. All participants were seeking an evaluation for ADHD (age M = 32.48, SD = 12.38; 55% male, 69% Caucasian). Participants completed the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID Part I). On the CAADID, participants endorsed whether or not they were described by parents or others as having any of 13 temperamental risk factors in infancy and toddlerhood.

**Results:** Logistic regressions were performed to ascertain the effects of retrospective self-report ratings of childhood temperament on ADHD diagnostic status in adulthood. Retrospectively endorsing any of the following early temperamental characteristics significantly increased one's likelihood of being diagnosed with ADHD in adulthood relative to those who did not endorse these factors: high activity level, impulsivity, fearfulness, accident prone, short attention span, irritability, poor adaptation to change, frequent temper tantrums, sleep problems, and clumsiness. Moreover, of those adults who were diagnosed with ADHD, endorsement of a high activity level, impulsivity, being accident prone, a short attention span, and clumsiness significantly increased the likelihood of receiving a diagnosis of ADHD, Predominantly Hyperactive-Impulsive or ADHD, Combined Presentation versus ADHD, Predominantly Inattentive Presentation. Relatedly, ADHD adults were significantly more likely to be diagnosed with comorbid disorders if they retrospectively reported being fearful or demonstrating poor adaptation to change.

**Conclusions:** Findings from the current study address a major gap in the relationship between temperament and ADHD. Specifically, we extended prior research focused on the role of early temperament in predicting the diagnosis of ADHD to an adult clinical population. Results indicated that retrospective self-report of several early temperamental factors significantly predicted not only ADHD diagnosis, but also the specific subtype of ADHD as well as the diagnosis of a comorbid disorder. This study highlights the importance of the inclusion of ratings of early temperament in clinicians' diagnostic assessment of ADHD and comorbid disorders. Notably, this is the first study of its kind to utilize retrospective ratings of early temperament. However, given the limits of retrospective report, future studies should include a longitudinal design to prospectively obtain early temperamental ratings so as to determine the true predictive utility of these factors on the later diagnosis of ADHD and comorbid disorders.

## **\*\*S20. MACHINE-LEARNING PREDICTION OF COMORBID SUBSTANCE USE DISORDERS IN ADHD YOUTH USING SWEDISH REGISTRY DATA**

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**Background:** Substance use disorders (SUDs) are associated with many adverse health and social consequences. Children with attention deficit hyperactivity (ADHD) have higher risk for SUD. Early identification of at-risk youth can help more targeted allocation of resources for more effective preventions and interventions.

**Methods:** In this study, we used Swedish registry records of children who were born between 1989 and 1993 to train machine-learning models for SUD prediction in ADHD youth. We used family, perinatal, medical, criminal and educational information of the children and their immediate family members that were available up to index child age 17 to predict if the child will develop SUD between age 18 and 20. 19653 ADHD children were obtained and used in the study. We randomly divided the sample to training (70%), validation (15%) and held-out

test set(15%). We used validation set to tune the hyperparameters of five different classification models including support vector machine (SVM), K-Nearest Neighbors (KNN), and gradient boosting (GB), random forest (RF) and multi-layer perceptron (MLP). The best models were then tested on the held-out test samples.

**Results:** RF and MLP models achieved similarly moderate accuracies with the area under the receiver operating characteristic curve (AUC) 0.75. We used conditional probability analyses to illustrate the potential clinical utility of our prediction models. We also identified the most influential predictors for developing SUD in youth, which highlighted the roles of educational attainment, socioeconomic status and family stress in SUD risks.

**Conclusions:** Our results suggest that population registry data may, one day, provide useful algorithms for predicting the at-risk youth for SUDs and, perhaps, other comorbid conditions of ADHD. Future work should focus on improving the features used for more accurate predictions. Given the large dataset available in the population registries, it is also possible that applying other machine learning algorithms may improve model performance.

## **S21. Gender Differences in ADHD Subtype Distribution in the Puerto Rican Youth Population**

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**Background:** Researchers have shown a growing interest in understanding gender differences in Attention-Deficit Hyperactivity Disorder (ADHD). While studies in referred samples have found a ratio of boys to girls with ADHD as high as 10:1, epidemiological studies have found a lower ratio of approximately 2:1. This suggests the presence of biases in referral and diagnosis and raises questions about differences in symptomatology across genders. Girls, conventionally, are believed to suffer from more inattention than hyperactivity, but attempts to clarify the distribution of ADHD subtypes across genders have rendered mixed results.

Further complicating this work, there is evidence that the distribution of ADHD subtypes (Inattentive, Hyperactive, and Combined), varies by age and country, and that the prevalence of ADHD is rising in the Latino population, and among girls. These findings highlight the importance of research focused on these populations. A proper understanding of gender differences in ADHD will inform diagnosis and clinical care and may clarify the etiology of the condition. In this study, we analyze the distribution of ADHD and its subtypes across gender in the Boricua Youth Study (BYS), a cohort study examining psychopathology in children and adolescents of Puerto Rican descent living in Puerto Rico or New York City.

**Methods:** A multi-stage probability sample of Puerto Rican children (ages 5-15) was obtained for the south Bronx and two metropolitan areas in Puerto Rico. Children were assessed using the Diagnostic Interview Schedule for Children-IV (DISC-IV). ADHD status and subtype were assigned according to DSM-5 criteria. Weighted multiple logistic regression was used to assess the relationship between ADHD diagnosis (outcome) and gender and site (predictors) while adjusting for age, disruptive behavior disorder (DBD), and public assistance. Similarly, a sub-analysis was conducted solely on participants diagnosed with ADHD to assess for gender differences in distribution of subtypes.

**Results:** Children (n=237) were diagnosed with ADHD across both sites (Bronx n=1,138, Puerto Rico n=1,353). Girls were less likely to be diagnosed with ADHD overall (boys=166, girls=71, adjusted OR: 0.53, CI: 0.34-0.85). Relative to boys with ADHD, girls with ADHD were less likely to have the combined subtype (aOR: 0.46, CI: 0.22-0.96), and tended to be

more likely to have the inattentive (aOR: 1.07, CI: 0.5-2.29) and hyperactive subtype (aOR: 1.91, CI: 0.97-3.75). Children with ADHD in Puerto Rico were more likely to have the hyperactive subtype compared to children in the south Bronx (aOR: 2.00, CI: 1.1-3.64).

**Conclusions:** In concordance with the existing literature, girls in the BYS cohort were less likely to be diagnosed with ADHD overall and among those with ADHD, girls relative to boys were less likely to have the combined subtype. Though not statistically significant, females tended to have the inattentive and hyperactive subtypes, contrary to existing literature. Our findings are somewhat consistent with the conventional view that girls are more likely to suffer from inattention. The finding that a smaller proportion of girls than boys suffered from ADHD combined subtype may be attributable to girls suffering from fewer ADHD symptoms as ADHD-C requires a greater symptom burden. The larger proportion of children with ADHD-HI in Puerto Rico may be related to the influence of unique local factors, such as access to service or medication use, that may favor the diagnosis.

## **S22. HOW ADHD SYMPTOMS RELATE TO WORD READING AND READING COMPREHENSION**

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**Background:** Attention Deficit Hyperactivity Disorder (ADHD) and reading disabilities (RD) are among the most common learning challenges diagnosed in the United States (Shaywitz & Shaywitz, 2003; Visser et al., 2014). In addition, the two have a comorbidity rate that is reported to be between 10-40% (Willcutt et al., 2010). Both groups also demonstrate deficits in executive functions (EF), which are considered the general-purpose control mechanisms that coordinate the various sub processes of human cognition, including attention (Carretti, Borella, Cornoldi, & De Beni, 2009; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Miyake et al., 2000). However, RDs are not homogeneous, so it is important for researchers and practitioners to understand how ADHD attention symptoms relate to specific reading processes. Studies of reading ability tend to implicate EF in aspects of reading comprehension more than in word-level reading. Thus, if ADHD and RD are co-diagnosed at least in part due to their shared EF deficits, then it is possible that the reading skill most highly impacted by ADHD is reading comprehension. We investigated the relationships among ADHD attention symptoms, reading comprehension, word reading, and EF and to answer the following questions: (1) Are ADHD attention symptoms more highly associated with reading comprehension than with word reading? (2) If yes, does EF mediate the relationship between these symptoms and reading comprehension?

**Methods:** As attentional control and reading skills in the general population appear to be normally distributed, with ADHD and RD appearing at the low end of the continuum (Levy, Hay, McStephen, Wood, & Waldman, 1997; Shaywitz, Escobar, Shaywitz, Fletcher, & Makuch, 1992), our sample (n=296, fifth graders) was not limited to individuals with a clinical diagnosis, but rather included a broad range of reading and attentional profiles. Due to the nested nature of our data (students in classrooms), we tested our hypotheses using Hierarchical Linear Modeling (Raudenbush & Bryk, 2002), which accounts for within-classroom variation. First, the relationships among ADHD symptoms, word reading, and comprehension was estimated with the following equation:  $ADHD\ Attention\ Symptoms_{ij} = \gamma_{00} + \gamma_{10} * Word\ Reading_{ij} + \gamma_{20} * Comprehension_{ij} + u_{0j} + r_{ij}$ . A general linear hypothesis test ( $\chi^2$ ) was conducted to examine whether the strength of the relationship between reading comprehension and ADHD symptoms was significantly stronger than that between word reading and ADHD

symptoms. Finally, a mediation model was constructed, which included our measure of EF:  $ADHD\ Attention\ Symptoms_{ij} = \gamma_{00} + \gamma_{10} * EF_{ij} + \gamma_{20} * Word\ Reading_{ij} + \gamma_{30} * Comprehension_{ij} + u_{0j} + r_{ij}$ .

**Results:** Supporting our hypothesis, we found that ADHD symptoms were significantly related to both word reading ( $b = 0.02, p < 0.001$ ) and reading comprehension ( $b = 0.04, p < 0.001$ ), but that the strength of the relationship between ADHD symptoms and reading comprehension was significantly stronger than the relationship between ADHD symptoms and word reading ( $\chi^2(1, N = 281) = 52.86, p < 0.001$ ), and that the former was partially mediated by EF (direct effect between ADHD symptoms and reading comprehension:  $b = 0.03, p = 0.005$ ). Our findings suggest that even small changes in ADHD symptoms may have a large impact on a child's reading comprehension ability.

**Conclusions:** We discuss how our findings impact our scientific understanding of the comorbidity of ADHD and RD, and how they may also impact screening, diagnostic, and instructional practices.

### **S23. INVESTIGATING THE RELATIONSHIP BETWEEN OBJECTIVE AND SUBJECTIVE EVALUATIONS OF TREATMENT OPTIMIZATION IN INDIVIDUALS WITH ADHD**

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<sup>1</sup>Carolina Attention Specialists

**Background:** Attention-Deficit/ Hyperactivity Disorder (ADHD) is associated with persistent and often life-long challenges (Michielsen et al., 2012). Fortunately, ADHD is a treatable disorder, with meta-analyses demonstrating statistically significant and clinically robust improvements in symptomatology following pharmacological treatment relative to placebo (Meszaros et al., 2009).

While standard clinical procedures typically involve self-rated evaluations of symptomatology as a means for measuring medication effects in adults with ADHD, research has demonstrated that patients often have difficulties assessing improvements in symptoms (Kooij, 2013). Objective measures of symptomatology, like QbTest, have been seen to yield valuable and unique information to the otherwise subjective assessment of medication effects in adults with ADHD (Bijlenga et al., 2015). However, further research is needed in order to evaluate the associations between objective and subjective evaluations of adult ADHD pre- and post-treatment.

**Methods:** Adult ADHD patients from Carolina Attention Specialists who had agreed to pharmacological treatment were included in the study. Subjective (ASRS, NPQ) and objective (QbTest) measures were collected at i) baseline (N = 49), ii) follow-up 1 (N = 49), and iii) follow-up 2 (N = 33).

**Results:** Relative to baseline levels, statistically significant improvements in subjective and objective measures of ADHD were observed at follow-up 1 ( $ps < .001$ ). Further improvements at follow-up 2 were only observed for objective measures of hyperactivity ( $p < .05$ ) and inattention ( $p < .05$ ). Correlation analyses revealed no significant correlations between subjective and objective evaluations at baseline. The reverse was found after treatment initiation, with analyses demonstrating significant positive correlations ranging from .31 to .45 between subjective and objective measures ( $ps < .05$ ).

**Conclusions:** Preliminary analyses indicate that while both subjective and objective measures of ADHD can capture initial improvements in symptoms, objective measures may be more sensitive to longer-term improvements following titration/changes in medication. Further, our



findings suggest that subjective and objective measures show better consistency when evaluating treatment effects than at baseline. It is anticipated that the analysis of additional follow-up 2 and long-term follow-up data will shed further light into the associations between objective and subjective measures of symptomatology in adults with ADHD.

## **S24. UNDETECTED PTSD IN A CLINICAL POPULATION OF ADULTS WITH ADHD**

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**Background:** Many patients will undergo treatment for mood and anxiety disorders, however, see no improvements in their symptoms. Recent research has shown that within treatment-resistant depression and treatment-resistant anxiety populations, undetected ADHD is present in 32% of cases (Sternat et al., 2018; GAD-TRD poster?). Furthermore, antecedent ADHD has been shown to be a significant risk factor in the development of PTSD following exposure to trauma (Adler et al., 2004; Biederman et al., 2014). The following study uses patients referred to a tertiary-care clinic, predominately with a treatment-resistant mood or anxiety disorder, and aims to assess whether those who meet criteria for ADHD have a greater likelihood of the presence of an undetected trauma.

**Methods:** Data was collected from referrals, over the last three years (N=126), of a tertiary-care mood and anxiety clinic. Patients were referred for predominately treatment resistant mood and anxiety disorders. Upon intake, referrals were assessed for primary diagnoses, number of diagnoses, and medication history using the clinical-structured Mini International Neuropsychiatric Interview (M.I.N.I. Plus 5.0.0). A retrospective one-way analysis of variance was conducted to compare number of undetected PTSD diagnoses in ADHD versus non-ADHD populations.

**Results:** The results of this preliminary analysis, show that within a clinical population with predominately treatment resistant mood and anxiety patients, there was a significant difference between comorbid ADHD versus non-ADHD groups in PTSD diagnoses,  $F(1, 73) = 4.56, p = .04$ . That is, the ADHD group had a greater number of undetected PTSD diagnoses.

**Conclusions:** The results of the preliminary analysis demonstrate that the presence of ADHD in our clinical population, increases the likelihood of a PTSD diagnoses. This suggests that within our complex mood and anxiety referrals, who had previously undergone treatment with either psychiatric medication or psychotherapy, the presence of an undetected comorbid diagnosis of PTSD and ADHD may contribute to remitting symptoms. Thus, treatment focused on underlying ADHD and trauma may contribute to better outcomes for treatment resistant mood and anxiety disorders.

## **S25. SELF-PERCEIVED CHARACTER STRENGTHS OF YOUTH WITH ADHD**

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**Background:** Self-esteem among adolescents with Attention Deficit Hyperactivity Disorder (ADHD) is of critical concern to clinicians, educators, and parents. Youth with ADHD are more likely than their typically developing peers to report low self-esteem (Sawyer et al., 2002), which can lead to poor long-term mental and physical health, social maladjustment, and

fewer academic and economic prospects (Trzesniewski et al., 2006). In order to disrupt the negative trajectories associated with low-esteem, a growing body of literature from positive psychology suggests to focus on the development of adolescents' strengths and abilities (Shogren et al., 2006). The first step in providing strengths-based support for youth with ADHD is identifying the unique skills of this population. The Values in Action Inventory for Youth (VIA-Youth) is a valid, suitable measure to assess adolescents' self-perceived strengths of character (Park & Peterson, 2006). Moreover, the VIA-Youth Survey has been used as a strength-based assessment in prior research with adolescents with disabilities, including junior and senior high students with learning disabilities and intellectual disabilities (Shogren et al., 2006).

**Methods:** In the present research, adolescents with and without ADHD, ages 10-18, (current n = 43, goal n = 60, mean age = 13.4 years, female = 41.8%) completed the VIA-Youth Survey as a part of a larger, exploratory study examining the development of cognitive control and creativity. The results of the present study focused on the four strengths that the participants of each group ranked as most representative of who they are and what they value.

**Results:** Results revealed that, across both typically developing youth and youth with ADHD, love and kindness were given the highest rankings. Differences between the two groups arose when examining the character strengths given the third and fourth rankings. Typically developing youth rated zest and gratitude as their signature strengths, whereas youth with ADHD choose appreciation of beauty and excellence and creativity. According to the VIA classification system, these findings suggest that youth with ADHD are unique in their admiration for meaning encountered in the diversity of life experiences—"from nature to art to mathematics to science." They also indicate that youth with ADHD are set apart by their desire to be original thinkers and their ability to generate novel, constructive ideas (VIA Institute on Character, 2004).

**Conclusions:** Serendipitously, these results dovetail with prior research demonstrating enhanced creative abilities among adults with ADHD. Specifically, adults with ADHD outperform adults without ADHD on tasks requiring divergent, "out-of-the-box" thinking (White & Shah, 2006). Hence, creativity emerges as potential skillset to be incorporated in strengths-based interventions. As creativity is considered a premiere 21st century (Kliebecker et al., 2016), targeted creativity interventions have the potential not only to bolster self-esteem in youth with ADHD, but also to improve long-term social, academic, and economic adjustment amongst this population.

## **S26. OUTCOMES OF NONMEDICAL USE OF ADHD STIMULANTS: RESULTS OF A COMPREHENSIVE REVIEW**

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**Background:** The efficacy of prescription stimulants for the treatment of ADHD is well established; however, these medications have potential for abuse and misuse. The nonmedical use (NMU) of prescription stimulants, which includes abuse and misuse, is a prevalent and growing problem. In 2016, 1.4 million individuals aged  $\geq 12$  years in the United States initiated NMU of prescription stimulants. [1] Understanding NMU outcomes is crucial for healthcare providers to educate both patients and caregivers and to inform public policies about the proper

use of prescription stimulants. Here, we report the outcomes of NMU of prescription stimulants identified through a comprehensive review of the literature.

**Methods:** We systematically searched PubMed, PsycINFO, and SCOPUS databases from inception to May 2018 for studies containing empirical data about NMU (includes abuse and misuse), malingering of ADHD, and diversion of prescription stimulants. Additional references identified by the authors were also assessed for inclusion. Studies that looked at outcomes of prescription stimulant NMU are reviewed here.

**Results:** 109 studies met inclusion criteria; 25 of these studies reported on outcomes of prescription stimulant NMU. Data from the Drug Abuse Warning Network revealed that the number of emergency department visits by adults related to NMU of prescription stimulants increased nearly 200%, from 5,212 in 2005 to 15,585 in 2010. American Association of Poison Control Centers (AAPCC) data (N=15,876) showed that rates of healthcare facility admission were higher in cases of prescription stimulant NMU (intravenous [IV], 68%; nasal, 49%; oral, 65%) versus no NMU (22%). AAPCC data also showed that the risks of adverse medical outcomes were higher in cases of NMU versus no NMU. Mean number of adverse clinical effects was highest in the IV group (2.95), followed by the nasal (2.46), oral (2.17), and non-abuse groups (1.57). Odds of dying were greater for nasal (3/598 [0.5%]) and IV groups (2/164 [1.2%]) versus the non-abuse group (1/3,953 [0.03%]). Prescription stimulant exposures (both intentional and unintentional) were associated with moderate medical effects (defined as pronounced, prolonged symptoms) in 8.0%–36.5% of cases, major effects (symptoms that are life-threatening or produce significant disability or disfigurement) in 0.2%–5.8% of cases, and death in <0.1% of cases. Results of several studies of college students showed that frequently self-reported unwanted physiological effects of NMU of prescription stimulants include reduced appetite (63%–88%), sleep difficulties (49%–71%), irritability (29%–52%), headache (18%–51%), feeling sad (14%–40%), dizziness (11%–34%), and stomach ache (6%–32%). Eight studies of regional and national US databases found evidence that prescription stimulant NMU places substantial burden on healthcare facility utilization, which has increased over the past 25 years.

**Conclusions:** NMU of prescription stimulants, whether taken orally or non-orally, carries risks for serious adverse medical outcomes in some cases; these risks increase when stimulants are taken non-orally. However, data detailing the outcomes of non-oral prescription stimulant NMU are limited, and additional studies are needed. Educating patients and caregivers on the outcomes of prescription stimulant NMU, and reducing the occurrence of NMU, are important clinical objectives.

Reference:

1. Chen LY, et al. *J Clin Psychiatry*. 2016;77:e297–304.

## **\*\*S27. MOTIVATIONS AND BEHAVIORS OF NON-MEDICAL USE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) MEDICATIONS AMONG ADULTS**

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**Background:** 9.4% of children under the age 17 years and 4.4% of adults age 18-44 in the US have been diagnosed with ADHD. Prescription stimulant medications are an important and effective treatment option for many of these patients, however recent trends indicate a rise in non-medical use (NMU), defined as any use other than prescribed, including misuse/abuse and

use via non-oral routes. This study sought to evaluate the prevalence of ADHD medication NMU in US adults and the level of associated risk.

**Methods:** An online survey of the general US population was conducted during August-September 2018 in adults age 18-49 years to characterize ADHD diagnosis, prescribed medications, NMU of ADHD medications, routes of administration, and motivations for use.

**Results:** Of 12,000 respondents, 1207 (10.1%) reported having been diagnosed with ADHD. One-third of those diagnosed (n=803) had ever taken a prescription stimulant medication to prevent or treat their ADHD symptoms. 24.9% (301 of 1207) reported NMU of a prescription stimulant (with or without their own prescription). Of those diagnosed with ADHD, 9.2% had exaggerated or lied about symptoms to get a doctor to prescribe ADHD medication and 19.1% intentionally took more ADHD medication than prescribed. The primary motivations for taking more than prescribed were: to self-treat ADHD (regular dose was not working) 30.1%, enhance performance at work or school 27.5%, for energy 10.5%, to get high 7.8% or to improve mood or elevate spirit 7.2%.

Of those that had ever taken a prescription stimulant medication for ADHD, 145 (18.1%) reported modifying their ADHD medication. This included 73 (9.1%) respondents that reported non-oral use (snort, smoke, or inject). Modified use included 10.8% chewing prior to swallowing, 8.5% dissolving in liquid prior to swallowing, 8.2% snorting, 4.2% smoking, and 1.7% injecting (responses are not mutually exclusive). Motivations for chewing/dissolving prior to swallowing were primarily due to difficulty swallowing whole pills (42.5% and 35.3%, respectively), however, intent to achieve better/faster effect of the medication on ADHD symptoms (21.8% and 17.6-25.0%, respectively) and faster/more intense high than swallowing the medication (8.0-13.8% and 11.8-17.6%, respectively) were also reported. Motivations for snorting suggested a different pattern with only 6.1% reporting difficulty swallowing whole pills. The most commonly reported motivation for snorting was to achieve a faster effect on ADHD symptoms (36.4%), faster high (33.3%), better effect on ADHD symptoms (27.3%), and more intense high (21.2%). Reasons for smoking were similar to snorting (better/faster effect on ADHD symptoms 17.6%, 32.4%; faster/more intense high 35.3%, 20.6%). A small number of respondents reported injecting to achieve a better/faster high (n=4 (28.6%), n=2 (14.3%)) and for a faster/more intense high (n=4 (28.6%), n=3 (21.4%)).

**Conclusions:** NMU of ADHD medications is characterized by reports of motivations directed at performance enhancement as well as psychotropic effects (e.g. improve mood, get high). These data confirm that prescription stimulant medications are being manipulated to improve therapeutic, non-therapeutic, as well as euphoric effects. These findings support recent concerns by FDA and other regulatory agencies which identify prescription stimulants as emerging drugs of abuse. Awareness of the potential modified use of these medications is important for healthcare providers and their patients.

## **S28. EXPECTANCIES FOR THE EFFECTS OF STIMULANT MEDICATION BY ADOLESCENTS IN PEDIATRIC PRIMARY CARE TREATMENT FOR ADHD**

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**Background:** Expectations about the positive and negative consequences of using various abusable substances is known to predict adolescent drug and alcohol use. Research on expectancies has been extended to college students and their expected effects of stimulant medication use, but studies have not investigated these expectancies for adolescents or specifically for individuals prescribed stimulant medications for ADHD. The current study reports these expectancies and the degree to which clinical and stimulant diversion risk characteristics correlate with these expectations.

**Methods:** Data were from the baseline assessment of a randomized controlled trial of clinical practice strategies, versus routine care, for the prevention of stimulant medication diversion by adolescents stimulant-treated for ADHD in primary care. Patients were 13-18 years old (n = 341, Mage=14.96, 75% male, 84% white), and prescribed stimulant medication for ADHD at one of 7 pediatric practices. Respondents reported their expectancies about stimulant medication use by rating their agreement with the statement “ADHD medication is helpful for...” (1 = disagree, 5 = agree) for 24 items. Adolescents generally agreed that stimulants are helpful for ADHD symptoms and school performance (M=3.6-4.7); they generally disagreed that stimulants are helpful for non-intended treatment targets (e.g., controlling pain, getting high, treating people who don’t have ADHD, M=1.4-2.2). Their average rating was non-committal (M=2.9-3.1, “3=neither agree nor disagree”) for outcomes with unclear connections to stimulant treatment, but which are sometimes perceived as improved by stimulants or improved secondary to symptom improvement (e.g., preventing drug abuse, being more sociable). Three subscales were formed from the items: ADHD Symptoms (e.g., Being less impulsive, paying attention; M(SD) = 3.98(.74),  $\alpha$ =.78), Secondary Effects (M(SD) = 3.01(.87),  $\alpha$ =.77), Academic Performance (e.g., Understanding school work better, memorizing information; M(SD) = 3.97(.85),  $\alpha$ =.85).

**Results:** Teens who reported stronger effects of stimulants on ADHD symptoms were less likely to miss taking their medication,  $r=-.12$ ,  $p<.05$ , perceived greater harm associated with non-prescribed stimulant use,  $r=.21$ ,  $p<.001$ , had lower intentions of diverting their stimulant medication,  $r=-.11$ ,  $p<.05$ , perceived their peers to be less tolerant of stimulant diversion,  $r=.11$ ,  $p<.05$ , were less likely to have peers who use stimulants,  $r=-.14$ ,  $p<.05$ , or pain pills,  $r=-.12$ ,  $p<.05$ , without a prescription, and were less likely to have schoolmates they perceived were diverting their stimulant medications,  $r=-.14$ ,  $p<.05$ . Perceived secondary benefits was associated with one variable: less perceived schoolmate diversion,  $r=-.11$ ,  $p<.05$ . Associations were not observed for demographic variables or years treated.

**Conclusions:** These findings suggest that adolescents have formed opinions about stimulant treatment that map reasonably well onto the evidence-based clinical targets for stimulant medications, but our findings also suggest variability in responses that may have implications for diversion risk. In particular, teens may have increased risk when they perceive stimulants to be less helpful for improving ADHD symptoms. Longitudinal study is needed to determine whether and why these beliefs may have prognostic benefit/prospective predictive utility for long-term medication utilization and stimulant diversion.

## **\*\*S29. THE ASSOCIATION BETWEEN MATERNAL ANTIEPILEPTIC DRUG USE DURING PREGNANCY AND OFFSPRING ADHD**

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**Background:** Clinical guidelines warn against antiepileptic drug (AED) use during pregnancy. These guidelines are based on research showing prenatal AED exposure results in neural and behavioral anomalies in rats and that AEDs cross the human placental barrier in humans. Moreover, prenatal exposure to AEDs, particularly valproate, is associated with offspring problems, including attention deficit/hyperactivity disorder (ADHD). However, there are critical unanswered questions regarding the observed associations. Specifically, researchers have been unable to 1) rule out alternative explanations for observed associations, including confounding by the condition for which AEDs were prescribed (e.g., epilepsy, bipolar disorder) and 2) estimate associations between several specific drugs and offspring outcomes with adequate precision. The current study aimed to address these two gaps in the literature.

**Methods:** To accomplish our aims, we utilized the largest sample to date. First, we analyzed data from cohort of N=612,707 individuals born from 2006-2011 and followed through 2013. We examined the associations between maternal filled prescriptions of any AED in pregnancy and offspring ADHD and between paternal filled prescriptions and offspring ADHD. Paternal filled prescriptions were used to gauge the role of familial confounding because a teratogenic effect between paternal AED use during pregnancy and offspring ADHD is unlikely, but paternal use shares similar confounding factors with maternal use.

Second, we analyzed data from a cohort of N=1,485,724 individuals born in Sweden from 1996-2011 and followed through 2013 to estimate associations with lamotrigine, carbamazepine, and valproate. Because information on filled prescriptions is only available from 2006, we utilized this larger cohort with information on maternal-reported use of AEDs to examine associations with specific medications. These models were estimated with adjustment for many important confounders that past research has been unable to account for, including maternal and paternal factors (e.g., epilepsy, bipolar).

**Results:** First, maternal filled prescriptions were associated with offspring ADHD (Hazard Ratio=3.21, 95% CI=2.37-4.34). However, paternal filled prescriptions were also associated with offspring ADHD (HR=1.89, 95% CI=1.37-2.61). These findings suggest that associations are at least partially due to unmeasured familial confounding, though the differences between magnitudes is consistent with a causal effect of prenatal exposure to AEDs.

Second, we observed associations between maternal report of AEDs, particularly valproate, and offspring ADHD (HRLamotrigine=1.33, 95% CI=0.96-1.86; HRCarbamazepine=1.19, 95% CI=0.96-1.48; HRValproate=1.79, 95% CI=1.38-2.32) while adjusting for numerous measured covariates, which greatly attenuated the magnitude of the associations compared to unadjusted estimates. Notably, associations with lamotrigine and carbamazepine should be interpreted with caution, as estimates could not be differentiated from the null hypothesis.

**Conclusions:** Taken together, these findings highlight the importance of ruling out alternative explanations for causal hypotheses. Future research is needed to clarify the nature of observed associations further, including 2) the use of additional designs to rule out confounding (e.g., severity) and 2) whether prenatal exposure to AEDs is associated with related offspring problems (e.g., malformations, ASD).

### **S30. TEMPORAL REWARD DISCOUNTING IN COLLEGE STUDENTS WITH ADHD**

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**Background:** Steep Temporal Discounting (TD), or strong preferences for smaller immediate rewards over larger delayed rewards, has been shown to be associated with ADHD in children, adolescents, and adults (Jackson & MacKillop, 2016; Patros et al., 2016). Steep TD may be viewed as an underlying mechanism for (some of the) ADHD symptoms. Here, we measured TD in a sample of college students with ADHD. We also assessed whether TD was correlated with executive functioning and academic functioning.

**Methods:** A hypothetical TD task was administered. Trials included choices between receiving \$100 after 1 year or smaller amounts (\$1-\$95) today. Participants were 39 college students: 19 with a diagnosis of ADHD combined or inattentive presentation type, and 20 typical students. Questionnaires included the Conners'-Adult-ADHD-Rating-Scale (CAARS), the Barkley-Deficits-in-Executive-Functions-Scale (BDEFS), and the Learning-And-Study-Strategies-Inventory (LASSI).

**Results:** Although the ADHD group as a whole did not show steeper TD than controls, DSM-IV Hyperactive-Impulsive symptoms, but not inattention symptoms, correlated with TD ( $r = .32$ ,  $p < .05$ ). TD correlated substantially with relatively weak Executive Functions (BDEFS): Self-Restraint ( $r = -.33$ ), Self-Regulation of Emotions ( $r = -.32$ ), Motivation ( $r = -.41$ ), Total EF ( $r = .37$ ), and ADHD-EF Index ( $r = -.33$ ). TD was not, or only weakly, associated with academic functioning (LASSI).

**Conclusions:** The findings suggest that steep TD may be a relevant underlying mechanism specifically for symptoms of hyperactivity-impulsivity in college students. The correlations between steep TD and weak EF suggest that executive functions such as self-restraint and motivation play a role in the ability/choice to wait for future rewards in this sample.

### **S31. TMS-EVOKED MOTOR CORTEX INHIBITION AND MODULATION: RELATIONSHIP TO ADHD SYMPTOM SEVERITY AND RESPONSE INHIBITION IN CHILDREN**

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**Background:** Children with Attention Deficit/Hyperactivity Disorder (ADHD) consistently demonstrate impaired inhibitory behavioral control. These observations have prompted investigations of Transcranial Magnetic Stimulation (TMS)-evoked inhibition of the motor evoked potential (MEP) in ADHD. Studies thus far have focused on examining short interval cortical inhibition (SICI) in resting motor cortex (M1). Findings consistently reveal reduced SICI in children with ADHD compared to typically developing (TD) peers, suggesting this and related M1 physiology measures may prove useful as biomarkers of impaired inhibitory control. It remains unexamined whether differences in SICI are also present during active states. The objective of this study was to address this gap, extending TMS examination to test for ADHD-associated differences in M1 physiology during motor response selection/inhibition.

**Methods:** M1 physiology was examined in 131 right-handed, 8-12 year old children: 66 children with ADHD (mean age 10.5 years, 43 boys) and 65 TD children (mean age 10.6 years, 42 boys). TMS was performed over left M1 during rest and during a modified "race-car" Slater-Hammel (SH) response inhibition task. The primary outcomes were MEP amplitudes and SICI at rest and during GO and STOP trials, evaluated using mixed, repeated models.

**Results:** Behavioral analyses from the SH task revealed GO responses were significantly slower ( $p=0.01$ ) and more variable ( $p=0.002$ ) in children with ADHD; with no group differences in Stop Signal Reaction Times (SSRTs). TMS analyses revealed children with ADHD showed less M1 SICI not only at rest ( $p=0.018$ ), but also during GO trials ( $p=0.031$ ) and STOP trials ( $p=0.017$ ). Consistent with prior TMS finding in healthy adults, we observed that M1 excitability was increased from rest during task engagement ( $p<0.0001$ ) in both groups of children. However, this up-modulation was less robust in children with ADHD ( $p = 0.04$ ). Further, for both children with ADHD and TD children, lesser up-modulation was associated with higher parent ratings (Conners-3) of hyperactive/impulsive behavior (both groups  $p<0.0001$ ) and inattentive behavior (ADHD,  $p<0.0001$ ; TD,  $p=0.02$ ) as well as slower SSRTs (ADHD,  $p=0.009$ ; TD  $p<0.0001$ )

**Conclusions:** Findings reveal that children with ADHD show anomalous M1 physiology, with less motor cortical inhibition at rest as well as active response selection and inhibition states. We also discovered that children with ADHD show less up-modulation of motor cortex excitability in transition from rest to active state, and, that for both children with ADHD and TD children, lesser up-modulation is robustly associated with higher ADHD behavioral ratings and poorer cognitive inhibitory control. The findings provide evidence supporting TMS measures of motor cortex excitability and inhibition as relevant biomarkers of ADHD behavior. Future study will help determine the utility of these biomarkers for guiding diagnosis and intervention.

### **S32. SENSITIVITY TO REWARD AND PUNISHMENT IN CHILDREN WITH ADHD: THE IMPACT OF COMORBID INTERNALIZING DISORDERS AND SEX**

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**Background:** Sensitivity to reward (SR) and punishment (SP) are neurobiologically based motivational traits thought to relate to externalizing and internalizing psychopathology, respectively. Attention-deficit/hyperactivity disorder (ADHD) is an externalizing disorder that frequently co-occurs with other externalizing and internalizing disorders. Motivational models of ADHD emphasize heightened SR with little consideration of SP, despite evidence that these motivational traits interact to produce behavior. Much of this work has been done with boys, precluding examination of potential gender differences. The current study examined whether questionnaire and performance-based measures of SR and SP are differentially elevated in children with ADHD with or without comorbid disorders compared to typically developing (TD) controls and the effects of sex.

**Methods:** Participants were children ages 8-12 with ADHD with or without comorbid oppositional defiant disorder (EXT-only group;  $n=69$ , 19 girls) and anxiety or depression (EXT+INT group;  $n=33$ , 9 girls) compared to TD controls ( $n=75$ , 31 girls). Parent and self-report ratings of SR and SP were obtained using established questionnaire measures. Participants also completed two delay discounting tasks involving choices between smaller immediate, and larger delayed rewards (money and game-time). A subset of the sample ( $n=85$ ) also completed the Point-Scoring Reaction Time Task (PSRT), an objective behavioral measure of SR and SP based on change in reaction time in the context of reward and punishment. For the questionnaire and PSRT measures of SR and SP, 3 Group (TD, EXT-only, EXT+INT) x 2 Sex x 2 Valence (SR, SP) analysis of variance (ANOVA) was conducted. For the delay discounting measures, separate 3 group x 2 sex ANOVAs were conducted.



**Results:** Parent-reported SR and SP differed across groups (Group x Valence,  $p=.017$ ), such that SR was elevated in ADHD, regardless of comorbidity or sex, compared to TD ( $ps<.001$ ), whereas SP was elevated only in the EXT+INT group ( $ps<.001$ ). Self-reported SR and SP also differed across groups, but this depended on sex (Group x Sex x Valence,  $p=.047$ ). Specifically, EXT-only girls showed heightened SR compared to TD girls ( $p=.005$ ) whereas SR did not differ between EXT+INT and TD girls ( $p=.669$ ) or among boys ( $ps>.253$ ). In contrast, EXT+INT boys showed heightened SP compared to TD boys ( $p=.001$ ) and EXT-only boys ( $p=.018$ ), whereas there were no group differences in SP for girls ( $ps>.578$ ). Comorbidity and gender also impacted performance-based measures. For the PSRT, a marginal Group x Valence interaction ( $p=.061$ ) indicated heightened SR in EXT-only compared to EXT+INT ( $p=.018$ ), that was driven by girls ( $p=.009$ ; boys  $p=.684$ ) with no group differences in SP ( $ps>.20$ ). For both delay discounting tasks, evidence of Group x Sex interactions ( $ps<.038$ ) indicated greater delay discounting among EXT-only girls, whereas EXT+INT girls did not differ from TD. There were no group differences in boys.

**Conclusions:** These analyses reveal an interesting and surprising impact of gender on the relationship between SR/SP on EXT/INT disorders in children with ADHD. Among girls with ADHD, heightened SR is associated with externalizing disorders and greater delay discounting. In contrast, among boys with ADHD, heightened SP is associated with comorbid internalizing disorders. These findings suggest that the motivational underpinnings of psychopathology and comorbidity with ADHD are different for boys and girls.

### **\*\*S33. PREVALENCE AND CORRELATES OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AMONG YOUTH WITH 16P11.2 COPY NUMBER VARIATION**

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**Background:** Attention-deficit/hyperactivity disorder (ADHD) is characterized by a phenotypic heterogeneity that complicates diagnosis, treatment and research. Some of this heterogeneity may be attributable to a complex genetic architecture, as ADHD's inheritance is thought to be the additive, polygenic result of diverse rare and common variants. Research that focuses on populations with specific rare copy number variants (CNVs) known to have relatively high penetrance for ADHD can reduce this genetic complexity, paving the way for an enhanced understanding of ADHD phenotypes. Youth with a 16p11.2 CNV constitute one such population. Deletions and duplications at 16p11.2 have been implicated in multiple neurodevelopmental disorders, including ADHD. The present study analyzed data from the Simons Variations in Individuals Project (VIP) cohort to identify the prevalence and correlates of ADHD among youth with 16p11.2 deletions, youth with 16p11.2 duplications, and their biological non-carrier siblings.

**Methods:** Subjects of interest ( $n = 233$ ) included all 16p11.2 deletion carriers ( $n = 104$ ), duplication carriers ( $n = 56$ ) and non-carrier siblings ( $n = 73$ ) under age 18 who were enrolled in phase 1 of the Simons VIP study and were assessed for ADHD using either the NIMH Diagnostic Interview Schedule for Young Children (DISC-YC) ( $n = 80$ ) or Diagnostic Interview Schedule for Children (DISC-IV) ( $n = 153$ ). 7 of these subjects were excluded due to missing data. The remaining 226 were analyzed using a binary logistic regression that included deletion status, duplication status, gender, age and full-scale IQ as predictors and ADHD diagnosis as outcome. Subsequent logistic regressions were conducted among deletion carriers only ( $n = 101$ ) and among duplication carriers only ( $n = 55$ ). Exploratory linear regressions using the initial set of predictors but with total symptom number, number of

hyperactive symptoms and number of inattentive symptoms as outcomes were conducted among the subset of youth assessed with the DISC-YC only, as symptom count data were not available for youth assessed with the DISC-IV.

**Results:** 22.77% of deletion carriers (23/101), 16.36% of duplication carriers (9/55), and 8.70% (6/69) of non-carrier siblings had an ADHD diagnosis. Among this entire sample, ADHD diagnosis was significantly predicted by deletion carrier status (OR 8.60, 95% CI 2.95 - 25.01,  $p = 0.0314$ ) and age in months (OR 10.94, 95% CI 10.85 - 11.01,  $p = 0.0167$ ). ADHD diagnosis was predicted at the  $p = 0.0889$  level by male gender (OR 5.48, 95% CI 2.62 - 11.48). Among deletion carriers only, no predictors were significant, though male gender was a predictor at a  $p = 0.0598$  level (OR 6.57, 95% CI 2.40 - 17.95). No predictors reached strict statistical significance among duplication carriers only, but age in months was a predictor at  $p = 0.0528$  (OR 6.94, 95% CI 6.84 - 7.04). In exploratory linear models of DISC-YC symptoms, no significant correlates of symptom number survived correction for multiple comparisons.

**Conclusions:** Youth carrying a 16p11.2 deletion may be at greater ADHD risk than 16p11.2 duplication carriers or non-carriers. Age and male gender are potential risk factors that warrant further research in 16p11.2 CNV carriers. As more youth with this and other rare CNVs are recruited by the Simons VIP study and other projects, limitations of sample size will be overcome, allowing for deeper phenotyping of ADHD in these unique populations.

### **S34. MIRROR OVERFLOW MOVEMENTS IN ADHD DUE TO PHYSIOLOGICAL IMMATURITY OF THE MOTOR SYSTEM**

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**Background:** Children with ADHD show developmentally atypical levels of mirror overflow movements—unintentional movements that occur in the body part symmetrically opposite an intentional, unilateral movement. Because mirror overflow correlates with ADHD behavioral symptoms, the study of motor mechanisms in the disorder may shed light on more complex cognitive control mechanisms. In this study, we were interested in evidence of developmental delay vs. deviant (atypical-at-any-age) brain physiology associated with mirror overflow. Movement-associated suppression of the beta frequency band (18-28 Hz) on EEG is a well-studied index of motor cortical activation. Because it has been shown to increase in overall magnitude with age, it is a plausible index of developmental processes. Based on the literature, we proposed that children with ADHD would show EEG evidence of developmental delay, compared with age-matched peers: specifically, affected children would have a decreased overall magnitude of beta suppression (event-related desynchronization; ERD), and the relationship between amount of mirror overflow and beta ERD would be similar across diagnostic groups.

**Methods:** We recorded EEG while 25 children with ADHD and 25 age-matched controls ( $p=0.36$ ), ages 8-12, performed a unilateral sequential finger-tapping paradigm. We measured overflow using electronic goniometers. Our primary relevant EEG measure was total beta ERD magnitude. In order to assess the role of diagnosis in the relationship between ERD and measured overflow, we performed a moderation analysis.

**Results:** Consistent with a developmental delay account, children with ADHD showed an overall decreased magnitude of beta ERD ( $d=-0.629$ ,  $p=0.031$ ), and higher amounts of total overflow ( $d=-0.883$ ,  $p=0.003$ ). There was a significant inverse correlation between beta ERD and overflow in TD children ( $r=-.51$ ,  $p=0.008$ ); this correlation reached trend level in the ADHD group ( $r=-0.33$ ,  $p=0.1$ ). Moderation analysis showed no effect of diagnosis in the

relationship between beta ERD and overflow ( $p=0.73$ )—i.e., children with a certain magnitude of beta ERD have the same degree of overflow, no matter their diagnosis.

**Conclusions:** These results are consistent with a developmental-delay account of mirror overflow in ADHD and show no evidence for a deviant pattern. Specifically, both groups independently show a correlation between beta ERD and overflow. Further, children with ADHD show a decreased amount of beta ERD; the literature suggests younger children may show less beta ERD than older individuals. Finally, moderation analysis fails to show evidence for additional, diagnostic-specific factors which would be consistent with a deviant account. Stronger evidence for the proposition that mirror overflow results from the delayed development of motor control physiology would come from proper longitudinal studies. Further, given the known relationship between beta ERD and GABA, direct studies of this neurotransmitter (e.g., via TMS and MR spectroscopy) could prove to be an important mechanistic target in these longitudinal studies.

### **\*\*S35. A PILOT MRI STUDY OF BRAIN-BASED IRON CONCENTRATIONS' RELATION TO ATTENTION AND COGNITIVE CONTROL**

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**Background:** Emerging research implicates iron deficiency in childhood externalizing disorders featuring difficulties with attention and cognitive control, such as Attention-Deficit/Hyperactivity Disorder (ADHD). In children, this may be due to iron's critical role in the synthesis and expression of important neurotransmitters; thus impeding the functional development of the striatum, and the myelination of the frontal lobes. Iron deficiency has also been linked with weaknesses in attention and cognitive control. Previous research has largely utilized blood-based iron measures; however, such peripheral iron measures may not accurately represent iron concentrations in the brain. Neuroimaging methodologies now allow for non-invasive mapping of tissue magnetic susceptibility differences (Quantitative Susceptibility Mapping; QSM), which correlate strongly with tissue iron concentrations in gray matter. The present pilot study is the first to demonstrate the feasibility of estimating brain-based iron concentrations in children under the age of 8 years using ultra-high field MRI (neuroimaging at 7 Tesla). It is also the only study to examine the association between brain-based iron concentrations and performance-based measures of attention and cognitive control.

**Methods:** Twelve participants ages 6 to 9 years ( $M = 7.51$ ,  $SD = .95$ ), 83% female, completed a blood draw, MRI, and focused neuropsychological assessment emphasizing attention and cognitive control. Their parents and teachers completed ratings of ADHD symptomatology using the ADHD Rating Scale 5. Serum ferritin levels were estimated from collected blood samples. Brain iron concentrations were estimated using QSM (whole brain with 1mm isotropic resolution). Analyses focused on the basal ganglia, specifically the globus pallidus, caudate nucleus, and substantia nigra, because these brain structures are among the most iron-rich deep nuclei and are hypothesized to be related to ADHD. Performance-based measures sensitive to attention included a Go/No-go task, the NIH Toolbox Flanker and Dimensional Change Card Sort tasks, and the Purdue Pegboard.

**Results:** Serum ferritin was not significantly associated with iron concentrations in the globus pallidus, caudate nucleus, or substantia nigra (all  $p > .05$ ). No significant relationships were observed between serum ferritin and: 1) parent/teacher ratings of inattention and hyperactivity/impulsivity, or 2) performance-based measures of attention. Conversely, estimates of iron concentration in the caudate nucleus were strongly negatively correlated with

teacher-rated hyperactive/impulsive symptoms ( $r = -.83$ ,  $p = .04$ ) and with a bimanual measure of fine motor speed and dexterity that is sensitive to attention (Purdue Pegboard,  $r = .57$ ,  $p = .05$ ). Iron concentrations in the globus pallidus and substantia nigra were not significantly associated with attention.

**Conclusions:** Findings of this pilot study suggest that: 1) children as young as 6 years old tolerate neuroimaging at 7 Tesla well with behavioral desensitization training, 2) brain iron concentrations can be reliably estimated in young children via QSM, and 3) these estimates may uniquely predict both behavior rating and performance-based measures of attention. The present study also lends support to the emerging body of research suggesting that blood- and brain-based iron concentrations may not be strongly related, and that the latter may offer greater predictive value with regards to cognitive functions such as attention.