2018 APSARD Annual Meeting

January 12-14, 2018

The Washington Marriott Wardman Park
Washington, D.C., USA

APSARD
The American Professional Society of ADHD and Related Disorders

Friday, January 12, 2018

Plenary Session
5:30 PM - 7:30 PM

1. ADHD AND COGNITION

Chair: Philip Asherson, Kings College London

Overall Abstract: This session will outline different models of cognitive and neural processes that underlie the symptoms, impairments and treatment response to medication in ADHD. The three speakers focus on different models of ADHD. First, Professor Asherson discusses the potential role of mind wandering as a core feature of the ADHD mental state, linked to aberrant regulation of default mode and salience network activity. This model is closely aligned to the default mode interference model and highlights early sensory deficits in addition to difficulties with executive control. Second, Professor Robbins discusses the role of noradrenaline and dopamine in sustained attention, working memory and impulse control; highlighting the lack of detailed information on the mechanisms by which changes in catecholamine functioning lead to the changes in cortico-striatal networks seen in ADHD. Finally, Professor Grace discusses in detail the paradoxical effects of stimulants in ADHD and controls. Dopamine system activity is characterized into two categories: the slowly changing, homeostatic low level tonic transmission, and the rapid, high-amplitude phasic transmission. These two types of transmission furthermore interact to modulate dopamine system responsivity and reduce symptoms such as inattention and hyperactivity when used to treat ADHD. Taken together, these talks provide state a state of the art update on contemporary models of ADHD and the treatment response to medication, highlighting the heterogeneity of the disorder, and areas for further research.

Learning Objectives:

- Understand the role of excessive spontaneous mind wandering in ADHD.
- Understand the role of executive control dysfunctions in ADHD.
- Understand the role of phasic and tonic dopamine neurotransmission and their relationship to ADHD and the treatment response to medication.
- Learn about key models of ADHD and the heterogeneity of processes underlying ADHD symptoms and the treatment response to medication.

1.1 ADHD AND THE WANDERING MIND: A NEW PERSPECTIVE ON INATTENTION IN ADHD

Philip Asherson, Kings College London

Abstract: Despite considerable progress in understanding the symptoms and impairments of ADHD and the availability of effective treatments, key clinical issues remain to be resolved. ADHD, particularly in adults, remains a disorder that often goes undiagnosed and untreated. Further progress in diagnosis, prevention and treatment is likely to require a better understanding of the underlying neural and cognitive mechanisms that lead directly to the symptoms and impairments of ADHD, and can be targeted by treatment interventions. Here we propose an approach that focuses on a measurable component of ADHD psychopathology,

excessive spontaneous mind wandering. We propose a new hypothesis for ADHD in which aberrant regulation of default mode and task-positive networks, leads to spontaneous mind wandering, which in turn leads to symptoms and impairments of ADHD.

Mind wandering (MW) occurs when one's mind drifts away from the primary task and focuses on internal, task-unrelated thoughts and images. MW is a universal experience that represents up to 50% of daily thinking time. While some forms of MW can be beneficial to individuals (e.g. strategic thinking about a grant proposal while driving a car), other forms can be detrimental (e.g. spontaneous uncontrolled thoughts that interfere with tasks such as listening to a lecture). These two types of MW have been referred to as deliberate MW and spontaneous MW respectively, and are thought to reflect a different balance of regulatory processes on internal self-generated thought. Spontaneous MW detrimental to performance has been proposed as a mechanism explaining many of the symptoms and impairments of ADHD, thought to reflect dysfunctional connectivity between the brain's default mode network (DMN) and task positive networks.

In our own studies, we developed a clinical scale reflecting ADHD patient reports of excessive spontaneous MW. The 12-item Mind Excessively Wandering Scale (MEWS) captures three characteristics of MW in ADHD: thoughts constantly on the go, thoughts flitting from one topic to another and multiple thoughts at the same time. Case-control comparisons in two independent samples revealed significantly elevated ratings of MW in ADHD, comparable to that found for rating scales of ADHD symptoms. In relation to impairment, MEWS scores were the strongest predictor of functional impairment, followed by inattention and hyperactivity/impulsivity, indicating the clinical relevance of MW as a predictor of impairment in daily life.

During this talk I will outline studies that link ADHD to MW, MW to default mode network activity (DMN), and DMN activity to ADHD. Together these studies raise the possibility that deficient regulation of DMN activity, leads to excessive spontaneous MW in ADHD. Further support for the potential importance of MW to ADHD comes from a series of observations that draw strong parallels between the processes that underlie the regulation of MW in neurotypical controls, and processes known to be deficient in ADHD. These parallels include: (1) context regulation of MW in controls and neural activity in ADHD; (2) sensitivity of MW and MW-associated neural processes to task salience and rewards; (3) perceptual decoupling of somatosensory processing during MW and in ADHD; (4) Impairments in cognitive task performance, and performance in daily life.

1.2 THE TRANSLATIONAL NEUROPSYCHOPHARMACOLOGY OF ADHD

Trevor Robbins, University of Cambridge

Abstract: Evidence from genetics and the pharmacological treatment of ADHD suggests that the catecholamine neurotransmitters dopamine (DA) and noradrenaline (NA), play an important role in the prominent symptoms of sustained attention, working memory and impulse control of this disorder. However, the possible aetiological influence of the catecholamines in ADHD symptoms remains undetermined and a detailed mechanistic understanding of stimulant drug therapy, in terms of the relative contributions of DA and NA across different cortico-striatal networks is lacking. Moreover, other factors such as structural brain changes also have to be taken into account. This talk will focus on the mechanisms underlying the therapeutic

actions of typical and atypical stimulant drugs by considering basic cognitive neuroscience studies in both animal and humans, including patients with ADHD. These studies suggest that there may be several components to the heterogeneous ADHD phenotype, depending on disruption of specific systems and their chemical neuromodulation, with important implications for the treatment of this disorder.

1.3 TONIC-PHASIC DOPAMINE REGULATION OF LIMBIC SYSTEM INTEGRATION IN THE PATHOPHYSIOLOGY AND TREATMENT OF ADHD

Anthony Grace, University of Pittsburgh

Abstract: A continuing quandary concerning the pathophysiology and treatment of Attention Deficit/Hyperactivity Disorder (ADHD) are the paradoxical effects of psychostimulants, in that these drugs produce hyperactivity and often confusion in normal subjects; on the other hand, in patients ADHD the same drugs cause a decrease in activity levels and a better focusing of attention. However, the way that the drugs are administered is likely to have a differential impact on systems involved in attention and cognition. Dopamine system activity is characterized into two categories: the slowly changing, homeostatic low level tonic transmission, and the rapid, high-amplitude phasic transmission. These two types of transmission furthermore interact to modulate dopamine system responsivity. Thus, phasic transmission is believed to represent the signaling event that increases attention to a stimulus, whereas tonic dopamine modulates phasic amplitude bidirectionally. Amphetamine given at high doses will amplify phasic transmission by amplifying the impact of rapid dopamine release via attenuation of synaptic uptake; this will lead to a nonselective potentiation of dopamine transmission and nonselectively distribute orientation of attention throughout the target areas. However, if given at low doses orally, the slow increase in extracellular dopamine produced will lead to a presynaptic attenuation of the phasic dopamine response, while altering the proportion of dopamine neurons active will lead to increased focused response to stimuli. As a result, there can be a combined increased focusing of attention while limiting background hyperactivity.

Saturday, January 13, 2018

Plenary Session

9:00 AM - 11:00 AM

2. NEW DATA ON TREATMENT OF ADHD AND IMPAIRMENTS IN ADULTHOOD

Chair: Frances Levin, Columbia University Medical Center

Overall Abstract: There is overwhelming evidence that ADHD increases the risk of substance use disorders (SUDs), as well other medical and psychiatric disorders. While early studies found that pharmacologic treatment of ADHD in childhood reduced the risk of adolescent substance use disorder, this was less evident as adolescents matured into adulthood. Dr. Wilens will present recent data, based on large survey, registry and clinical studies that have found that early childhood pharmacologic treatment prescribed for longer duration reduces the risk of substance use disorder in adolescence and early adulthood. Similar to SUDs, other harmful behaviors such as accidental injuries, eating pathology and tobacco use is associated with having ADHD. Based on data collected from the Milwaukee longitudinal study, Dr. Barkley will discuss how these adverse outcomes might impact on life expectancy. Finally, Dr. D'Onofrio will discuss how analyses of large-scale health insurance claims datasets in the US and national registry data in Sweden can elucidate how various adverse outcomes, such as serious substance use problems, accidents, other psychiatric comorbidities are associated with periods of dispensed/non-dispensed ADHD medications within individual comparisons. The implications of these data, both in terms of prevention and mitigating harmful outcomes into adulthood will be discussed.

Learning Objectives:

To learn what factors are associated with reduced risk of developing SUDS among those with ADHD.

- To become knowledgeable of the adverse health outcome associated with ADHD and the potential impact on longevity.
- To become familiar with the various large-scale datasets, survey data, and clinical longitudinal studies that may elucidate how the risk of SUD, and other health outcomes, may be mitigated by early intervention and ongoing treatment.

2.1 WHAT EFFECT DOES ADHD MEDICATION TREATMENT HAVE ON THE LATER RISK FOR SUBSTANCE USE DISORDERS?

Timothy Wilens, Massachusetts General Hospital

Abstract: *Objective*. ADHD is the most common neurobehavioral disorder presenting for treatment in childhood; and one of three most common chronic disorders treated by Pediatricians. Substance use disorders occur in approximately 10% of adolescents. ADHD has been shown to be a risk for the development of substance use disorders. The focus of this session is to focus on data that highlights the risk ADHD begets on SUD, and on the effect of stimulant and nonstimulant treatment of ADHD on the ultimate risk for SUD. *Methods*. Cross sectional, longitudinal, survey, clinical, registry, and metanalytic studies examining this issue will be described. Recent data derived from large survey and registry studies will be shown in

detail. *Results*. Longitudinal studies of ADHD youth growing up seem to show some protection from substance use in adolescents that is lost in adulthood. More recent larger survey and registry data support that treatment of ADHD reduces later SUD-in a duration of treatment related manner. *Conclusions*. The preponderance of recent data suggests that early treatment of ADHD results in reduced risk for SUD in adulthood.

2.2 HEALTH OUTCOMES OF ADHD: DO THEY ADVERSELY IMPACT LIFE EXPECTANCY?

Speaker: Russell Barkley, Virginia Commonwealth University Medical Center

Abstract: This presentation will focus on various health and medically related outcomes of ADHD such as accidental injuries and self-harm, substance use and abuse particularly tobacco and alcohol use, eating pathology, obesity and risk for coronary artery disease, and other factors known to have an adverse impact on not ongoing quality of life but life expectancy. Examples of adverse health outcomes will be drawn from the results of the Milwaukee longitudinal study of ADHD and more recent research studies by other investigators. From these, the impact on life expectancy will be computed using recently available formulas.

2.3 THE RISKS AND BENEFITS OF ADHD MEDICATION: A PHARMACOEPIDEMIOLOGIC PERSPECTIVE

Brian D'Onofrio, Indiana University

Abstract: Randomized controlled trials (RCTs) suggest that ADHD medication has beneficial short-term effects on symptoms of ADHD, and some co-occurring disorders. RCTs of ADHD medication have serious limitations, however, including the inability to generalize to individuals with serious comorbid problems, study rare-but-serious outcomes, and adequately examine long-term outcomes because treatments were only randomized for a relatively short periods of time. The increasing use of ADHD medications is being heavily debated, therefore, because of the uncertainty regarding both short-term and long-term effects of ADHD medications on serious outcomes, in addition to concerns of misuse and overuse. There is, therefore, a critical need to more precisely identify the specific risks and benefits of ADHD medication in the population, particularly with samples and designs that can explore rare outcomes. The presentation will provide examples of how the analyses of large-scale health insurance claims datasets in the United States and national registry data (e.g., in Sweden) can help specify the risks and benefits of ADHD medication when using advanced research designs. In particular, the talk will describe how the use of within-individual comparisons (i.e., using periods in which an individual is not dispensed medication as the comparison for periods in which he/she was dispensed medication) can help elucidate the associations between ADHD medication and numerous outcomes, including serious substance use problems, motor vehicle accidents, depression/suicide attempts, and accidents and injuries.

Lifetime Achievement Plenary Session

11:30 AM - 12:30 PM

3. LIFETIME ACHIEVEMENT PLENARY

Chair: Mark Stein, University of Washington

Overall Abstract: The 2018 Lifetime Achievement Award is presented to Professor Joseph A. Sergeant. This award recognizes Professor Sergeant's longstanding dedication to the ADHD field and his substantial achievements in building the science of ADHD and its treatment. Professor Sergeant was the developer of the Cognitive Energetic Model of ADHD, and has subsequently gone on to study various aspects linking clinical and neuropsychological mechanisms with brain function. He is also the founder of the European Network for Hyperkinetic Disorders (EUNETHYDIS), which has been a highly successful model of collaboration for collaborative research, training, and the development and dissemination of clinical guidelines. We are especially honored to have Professor Sergeant with us because of the impact Eunethydis has had on the recent growth and development of APSARD in the US. Professor Sergeant's talk will examine the very timely issue of ADHD as a brain-based neuropsychiatric disorder.

Learning Objectives:

- To highlight the study of brain behavior relationships in ADHD from childhood to adulthood.
- To provide an overview of how advances in neuroscience have led to increased understanding of ADHD throughout the world.

3.1 BRAIN STATES AND FUNCTIONS IN TRANSITIONING ADHD

Joseph Sergeant, Vrije Universiteit Amsterdam

Abstract: In this talk, I will review the current state of knowledge concerning brain development of children with ADHD as they transition through adolescence to adulthood and, in some cases, wane from a syndromatic condition to relatively typical functioning or maintain their clinical ADHD status.

Interest in the role of brain states on functioning is now new in developmental neuropsychopathology. Initial work by Kramer & Pollnow1 on the hyperkinetic syndrome recognized that, in children with what is now termed ADHD, their neurological functioning state was non-optimal. A formal model 2-3 demonstrated that functioning of ADHD individuals was strongly dependent on their behavioural state, which could be manipulated by factors such as: instructions, reward, rate of stimulus presentation, prior sleep and medication4.

With the advent of advanced neural imaging techniques and their widespread use in child psychopathology research, there has been identified both important brain loci5-6 involved in the transition from childhood ADHD through adolescence7-10 to adulthood and functional networks, which differentiate those who persist in their ADHD versus those who remit11-12. This imaging research can also be divided into two general domains. The first, in which subjects have to apply controlled, conscious processing13. The second area is concerned with when the brain enters an automatic processing state currently referred to as day-dreaming14. A complementary strategy has been to use neural imaging to trace both structural and functioning brain development in ADHD in controlled or automatic states in follow-up and longitudinal studies6,11. More recently, studies of emotional recognition, emotional processing and induction by reward have shown functional effects on brain loci/ networks in individuals with ADHD 15-22.

It will be argued that the above research findings suggest a neuro-functional conception of ADHD, whose outline is now beginning to emerge and will be discussed here.

References

1 Kramer, F. & Pollnow, H. (1933). Uber eine hyperkinetische Erkankung im Kindesalter. Montatsschrif fur Psychaitrie en Neurologie, 82, 1-40

2 Sanders, A.F. (1983). Towards a model of stress and human performance. Acta Psychologica, 53, 61-97.

3 Sergeant, J.A., Oosterlaan, J. & Meere, van der J.J. (1999). Information processing and energetic factors in Attention-Deficit/Hyperactivity Disorder. In: H.C. Quay & A. Hogan (Eds.) Handbook of Disruptive Behavior Disorders. Plenum Press: New York (pp 75-104).

4 Sergeant, J.A. (2005). Modelling Attention-Deficit/Hyperactivity Disorder: A Critical Appraisal of the Cognitive–Energetic. Biological Psychiatry, 57, 1248-1255.

5 Cubillo A, Halari R, Giampietro V, Taylor E, Rubia K. (2011). Fronto-striatal underactivation during interference inhibition and attention allocation in grown up children with attention deficit/hyperactivity disorder and persistent symptoms. Psychiatry Research, 193(1), 17-27.

6 Clerkin SM, Schulz KP, Berwid OG, Fan J, Newcorn JH, Tang CY, Halperin JM (2013). Thalamo-cortical activation and connectivity during response preparation in adults with persistent and remitted ADHD. American Journal Psychiatry, 170(9): 1011-1019

7 Mattfeld AT, Gabrieli JD, Biederman J, Spencer T, Brown A, Kotte A, Kagan E, Whitfield-Gabrieli S. (2014). Brain differences between persistent and remitted attention deficit hyperactivity disorder Brain.137, 2423-2428.

8 Sripada CS, Kessler D, Angstadt M. (2014). Lag in maturation of the brain's intrinsic functional architecture in attention deficit/ hyperactivity disorder. Proceedings National Academy Science U S A., 111(39), 14259-14264.

9 Shaw P, Malek M, Watson B, Greenstein D, de Rossi P, Sharp W. (2013). Trajectories of cerebral cortical development in childhood and adolescence and adult attention-deficit/hyperactivity disorder. Biological Psychiatry, 74 (8), 599-606.

10 Shaw P, De Rossi P, Watson B, Wharton A, Greenstein D, Raznahan A, Sharp W, Lerch JP, Chakravarty MM. (2014). Mapping the development of the basal ganglia in

children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry, 53 (7), 780-789.

11 Szekely E, Sudre GP, Sharp W, Leibenluft E, Shaw P. (2017). Defining the Neural Substrate of the Adult Outcome of Childhood ADHD: A Multimodal Neuroimaging Study of Response Inhibition. Am J Psychiatry. Jun 29: appiajp201716111313. doi: 10.1176/appi.ajp.2017.16111313. [Epub ahead of print].

13 Schulz KP, Li X, Clerkin SM, Fan J, Berwid OG, Newcorn JH, Halperin JM.(2017). Prefrontal and parietal correlates of cognitive control related to the adult outcome of attention-deficit/hyperactivity disorder diagnosed in childhood. Cortex., 90:1-11. doi: 10.1016/j.cortex.2017.01.019.

14 McCarthy H, Skokauskas N, Mulligan A, Donohoe G, Mullins D, Kelly J, Johnson K, Fagan A, Gill M, Meaney J, Frodl T (2013). Attention network hypoconnectivity with default and affective network hyperconnectivity in adults diagnosed with attention-deficit/hyperactivity disorder in childhood. JAMA Psychiatry, 70(12): 1329-1337.

15 Wetterling F, McCarthy H, Tozzi L, Skokauskas N, O'Doherty JP, Mulligan A, Meaney J, Fagan AJ, Gill M, Frodl T. (2015). Impaired Reward Processing in the Human Prefrontal Cortex Distinguishes Between Persistent and Remittent Attention Deficit Hyperactivity Disorder. Human Brain Mapping 36(11):4648-63.

16 von Rhein D, Cools R, Zwiers MP, van der Schaaf M, Franke B, Luman M, Oosterlaan J, Heslenfeld DJ, Hoekstra PJ, Hartman CA, Faraone SV, van Rooij D, van Dongen EV, Lojowska M, Mennes M, Buitelaar J. (2015). Increased neural responses to reward in adolescents and young adults with attention-deficit/hyperactivity disorder and their unaffected siblings. J Am Acad Child Adolesc Psychiatry, 54(5):394-402.

17 Frodl T, Stauber J, Schaaff N, Koutsouleris N, Scheuerecker J, Ewers M, Omerovic M, Opgen-Rhein M, Hampel H, Reiser M, Möller HJ, Meisenzahl E. (2010). Amygdala reduction in patients with ADHD compared with major depression and healthy volunteers. Acta Psychiatr Scand. 121(2):111-8.

18 Posner J, Nagel BJ, Maia TV, Mechling A, Oh M, Wang Z, Peterson BS (2011). Abnormal amygdalar activation and connectivity in adolescents with attention-deficit/hyperactivity disorder. Journal American Academy Child Adolescent Psychiatry; 50:828–837.

19 Ichikawa et al (2014). Hemodynamic response of children with attention-deficit and hyperactive disorder (ADHD) to emotional facial expressions. Neuropsychologica, 63, 51-58.

20 Karalunas, S.L., Fair, D., Musser, E.D., Aykes, K., Iyer, S.P., Nigg, J.T., 2014. Subtyping attention-deficit/hyperactivity disorder using temperament dimensions. JAMA Psychiatry 71, 1015.

21 Schulz KP, Bedard AC, Fan J, Clerkin SM, Dima D, et al. (2014) Emotional bias of cognitive control in adults with childhood attention-deficit/hyperactivity disorder. Neuroimage Clin 5: 1–9.

22 Ho NF, Chong JS, Koh HL, Koukouna E, Lee TS, Fung D, Lim CG, Zhou J. (2015). Intrinsic Affective Network Is Impaired in Children with Attention-Deficit/Hyperactivity Disorder. PLoS One. Sep 25; 10(9): e0139018.

Concurrent Symposia Sessions

2:30 PM - 4:30 PM

4. OUTSIDE THE PILL BOTTLE: ASSESSMENT AND MANAGEMENT OF ADULT ADHD

Chair: Mark Stein, University of Washington

Overall Abstract: While multimodal treatment and collaboration between prescribers and mental health providers is common in pediatric ADHD, psychosocial treatment and collaborative and integrative care models are still emerging. The workshop will highlight complexities, barriers, and lessons learned in managing the adult ADHD patient as perspectives on diagnosis, management, and treatment will be provided by several non-prescribing providers.

Learning Objectives:

- Increase familiarity with the presentation and evaluation of adults with ADHD, including role of testing.
- Describe psychotherapeutic approaches that compliment pharmacological interventions in the adult patient.
- Increase awareness of how ADHD presents in older adult compared to other age groups.

4.1 COLLABORATION BETWEEN PRESCRIBERS AND OTHER CLINICIANS IN MANAGING ADHD

Thomas Brown, Keck School of Medicine of University of Southern California

Abstract: Most clinicians who treat patients with ADHD are aware that with both children and adults, persistence of use of ADHD medication is often not consistent and for many, not of long duration. For many prescribers, follow-up is limited to very brief occasional medication checks. If they have sufficient information to do so, psychologists, clinical social workers, coaches and counselors may play an important role in helping prescribers to educate patients and their families about the uses and limitations of medications. They may also elicit

information from the patient and facilitate more effective communication between patient and the prescriber about medication problems and effectiveness.
This presentation will describe factors that impact patient adherence to medication treatment for adults with ADHD. Case examples will emphasize the importance of prescribers and other clinicians educating patients about how ADHD medications work and how they need to be fine-tuned to fit individual differences. Discussion will also include how such communication between professionals can be facilitated while protecting scope of practice considerations.

4.2 IF A NEUROPSYCHOLOGICAL EVALUATION IS NOT NEEDED FOR DIAGNOSIS, WHAT DOES IT ADD TO DIAGNOSIS AND TREATMENT OF ADHD?

Jeanette Wasserstein, Mt. Sinai Medical College

Abstract: Brief review of major neuropsychological findings in Adult ADHD, what can and cannot be definitively be said. Clinical examples of positive and negative contributions in diagnosis and care.
Concluding guidelines about referral questions and when evaluation should be sought out.

4.3 STILL DISTRACTED AFTER ALL THESE YEARS: EXPLORING THE WORLD OF ADHD AFTER AGE 60

Kathleen Nadeau, Chesapeake ADHD Center of Maryland

Abstract: Kathleen Nadeau will share her preliminary findings from her ongoing research on adults over age 60 with ADHD. She has interviewed over 60 adults to date as well as gathered data from these adults about ADHD challenges and patterns of daily functioning, She will describe the amazing variety of life stories from this unexplored ADHD population.

4.4 INTENTIONS INTO ACTIONS: CBT FOR ADULT ADHD

J. Russell Ramsay, University of Pennsylvania, Perelman School of Medicine

Abstract: A common problem in the treatment of adult ADHD is that the disorder itself interferes with follow through on and effective use of treatment recommendations, particularly the very coping skills that are central to effective management of ADHD. The aim of this session is to review how cognitive behavioral therapy (CBT) for adult ADHD continues to evolve to target the impairments that often interfere with treatment progress. In particular specific tactics designed to help patients implement the necessary coping skills outside the consulting room will be reviewed. The common clinical issue of procrastination will be used to illustrate specific interventions that are used to help adults with ADHD be better able to consistently engage in important endeavors and manage the effects of ADHD symptoms on their functioning.

5. ADHD AND TECHNOLOGY: THE OPPORTUNITIES AND PERILS

Chair: Russell Schachar, University of Toronto

Overall Abstract: Every new technology created by mankind seems to afford advantages and disadvantages to society as a whole. Many recent technological developments can negatively impact people's mental health. The internet can become an obsession to the point of addiction, overstimulation arising from mobile devices and games can adversely impact attention, cognition, and sleep and social media are reshaping the way we relate to one another. Each of these effects are of substantial importance to mental health professionals. Paradoxically, these same devices, computers and media allow access to large scale data that is providing unpresented new insights into the mechanism of mental illness, shaping new technology-based treatments for ADHD and creating new ways of communicating with our patients to promote positive health behaviors. ADHD scientists and practitioners have eagerly embraced these new technologies as this symposium will reveal. This symposium will address the potential of digital platforms to promote positive mental health in humans and over-stimulation in animals, the effectiveness of specially designed computer games for treating the cognitive manifestations of ADHD, and the utility of electronic medical records (EMR) for evaluation of cardiac adverse effects of antidepressants in youth and for assessment of adherence to stimulant treatment in ADHD.

Learning Objectives:

- Be able to describe the results of recent trials of cognitive remediation for ADHD.
- Illustrate how electronic medical records can be used to address important clinical questions in ADHD.
- Be able to describe the effects of excessive non-normative stimulation during infancy.

5.1 TECHNOLOGY, BIG DATA, AND PREDICTING BEHAVIORAL HEALTH MEASURES

Brenda Curtis, Perelman School of Medicine University of Pennsylvania

Abstract: Novel, freely accessible digital tools allow individuals to interact with the world, which may provide researchers with deep insights into their behavior and disease treatment. However, there is limited research on the potential of digital platforms to promote positive behavioral health outcomes and on which digital platforms are best to reach individuals. In this presentation, we will discuss the range of digital and mHealth technologies and their potential application in behavioral health research. We will also discuss privacy issues in this type of research.

5.2 DIGITAL THERAPEUTICS FOR THE TREATMENT OF ADHD: RESULTS FROM A LARGE-SCALE RANDOMIZED CLINICAL TRIAL

Scott Kollins, Duke University

Abstract: A wide range of technology-based products have been developed for the treatment of ADHD, though there is controversy regarding the scientific evidence supporting their use. This session will describe the design and results of a large-scale, FDA-registration clinical trial to evaluate the effects of a digital app for the treatment of ADHD. Focus will be given to the range of design considerations for these kinds of trials.

5.3 THE USE OF BIG DATA TO ADDRESS CLINICAL ISSUES

Joseph Biederman, Massachusetts General Hospital

Abstract: The advent of electronic medical records (EMR) has revolutionized the practice of medicine. It has also allowed its utilization for the evaluation of important clinical issues, relying on large data sets and objective metrics. The presentation will show two examples of utilization of EMR data: 1) the evaluation of cardiac adverse effects of antidepressants in youth; and 2) the assessment of adherence to stimulant treatment in ADHD. Results will show that antidepressants do not alter the QTc, and that contemporaneous rates of adherence to stimulant treatments for ADHD are very low.

5.4 EXCESSIVE NEWBORN STIMULATION AND SUBSEQUENT ATTENTIONAL CAPACITY

Dimitri Christakis, Seattle Children's Research Institute

Abstract: This presentation will summarize observational data from humans and experimental data from mice to make the case that excessive, non-normative sensory stimulation during critical periods of brain development can reduce attentional capacity in later childhood.

Sunday, January 14, 2018

Plenary Session
9:00 AM - 10:30 AM

6. GENETICS AND ENVIRONMENTAL FACTORS

Chair: Jeffrey Newcorn, Mount Sinai Medical Center

Overall Abstract: Although ADHD is a highly heritable disorder, simple genetic approaches have not been able to account for the disorder. Recent findings highlight the importance of complex genetic strategies and the aggregate effects of multiple genetic risk factors. There are also a number of well-documented environmental and psychosocial risk factors, which presumably augment, interact with and potentially modify genetic predisposition. This plenary session will explore genetic and environmental risk factors for ADHD, reviewing the latest findings regarding what is known about each. The session will additionally illustrate how recent genetic findings have been incorporated into large-scale epidemiologic studies (Thapar), and the longitudinal course of youth raised in extreme environments who suffered the effects of massive psychosocial deprivation (Sonuga-Barke).

Learning Objectives:

- Attendees will learn about genetic loci that have been implicated in ADHD, and how these can be used in clinical and epidemiological research.
- Attendees will learn about leading environmental causes of ADHD, and the impact of extreme deprivation on the development of ADHD symptoms.

6.1 ADHD: PROGRESS IN IDENTIFYING GENETIC AND ENVIRONMENTAL RISK FACTORS

Anita Thapar, Cardiff University

Abstract: Like other common health conditions, no single risk factor explains ADHD. Both genetic and environmental factors contribute risk and their effects are interdependent. It has been known for a long time that ADHD is familial and heritable. Molecular genetic discoveries are at last emerging. Rare, large effect size mutations as well as multiple common small effect size gene variants contribute to the genetic architecture of ADHD. Genetic findings also highlight that there is a biological as well as clinical overlap between ADHD and other neurodevelopmental and mental health problems. An interesting feature of ADHD is its variable developmental course. Genetic factors appear to contribute to these trajectories. ADHD is not explained by genes alone. There is a large literature documenting associations between ADHD and a wide variety of putative environmental risks. However, identifying what genetic and environmental risk factors are genuinely causal is challenging. Findings from research designs that go beyond simply testing for association are beginning to contest the robustness of some environmental exposures previously thought to be ADHD risk factors. Genetic discoveries are now beginning to be used to investigate environmental risks. These different research strategies are important because the robustness of findings has important implications for designing effective prevention and treatment strategies.

6.2 BEYOND HERITABILITY – HAVE STUDIES OF THE EFFECTS OF INSTITUTIONAL DEPRIVATION CHANGED HOW WE CONCEPTUALISE ADHD?

Edmund Sonuga-Barke, King's College London

Abstract: Recent studies have reported that ADHD clusters in families who have experienced social adversity and deprivation. Where family members are related biologically it is difficult to disentangle the causal effects of such environmental exposures from the genetic risks with which they are likely be correlated. Risk for ADHD is also substantially elevated in individuals exposed to deprivation in non-familial institutional settings. For instance, in the English Romanian Adoptees (ERA) study, adults exposed as children to between 6 and 43 months of extreme deprivation in the Romanian orphanages that existed at the time of fall of Communist regime prior to their adoption, displayed a 7-fold elevation of risk for ADHD. In this talk I will describe the ERA study and its key clinical findings – including those related to ADHD. I will explain how the study has provided a unique insight into the early environmental influences on neuro-development and mental health. With a special focus on our neuropsychological findings, I will also directly contrast ADHD that follows institutional deprivation and that seen in typical clinical cases. By so doing I will question where environmentally caused ADHD fits into current conceptualizations of the condition.

Plenary Session

11:00 AM - 12:30 PM

7. ADHD AS A BRAIN DISORDER: WHY IS THIS SO DIFFICULT TO ESTABLISH?

Chair: Stephen Faraone, SUNY Upstate Medical University

Overall Abstract: This plenary symposium will first briefly present the results of recent mega-analyses comparing brain volumes between ADHD patients and control participants. This will include previously published data about subcortical structures and new data about cortical structures. The controversy engendered by the subcortical publication will be described and then the plenary panel will present their views of the question "How do we view ADHD as a brain disorder in light of the ENIGMA ADHD results?" Each member of the panel will briefly present their views followed by a panel discussion and participation from the audience.

Learning Objectives:

- Learn about the results from the ENIGMA ADHD analysis of subcortical brain volumes.
- Learn about the results from the ENIGMA ADHD analysis of cortical brain volumes.
- Understand how the ENIGMA ADHD results inform us about the nature of brain abnormalities in ADHD.
- Understand the implications for future research.

Participants:

Barbara Franke, Radboud University Medical Center

Stephen Faraone, SUNY Upstate Medical University

John Gabrieli, Massachusetts Institute of Technology

Jay Giedd, University of California San Diego

Concurrent Lunch Discussion Groups

12:30 PM - 2:30 PM

8. INTERNATIONAL PERSPECTIVES ON ADHD

Chair: Margaret Weiss, University of Arkansas Medical Sciences

Overall Abstract: This symposium takes advantage of the presence of International leaders in the area of ADHD to open discussion about local strengths and challenges in the area of ADHD in different parts of the world. Each speaker will give a brief presentation of key strengths and challenges unique to their location, followed by open discussion of regional differences with audience participation.

Learning Objectives:

- Raise awareness of both the similarities and differences of ADHD in North America, Europe, Asia, the Middle East and the British Isles.
- Identify unique local challenges and strengths that can inform a knowledge exchange in which we learn from each other.
- Discuss collaborative initiatives to help grow a global network out of current national networks and facilitate global targets for improved care.

Participants:

Sandra Kooij, PsyQ, Program Adult ADHD, The Hague

Iris Manor, Geha MHC

Takuya Saito, Hokkaido University, Graduate School of Medicine

César Soutullo, University of Navarra Clinic

9. ADHD IN THE PRISON SYSTEM

Chair: Philip Asherson, Kings College London

Overall Abstract: This symposium will consider the impact of ADHD in relation to adult offending behaviour. Around 20-30% of prisoners are known to meet diagnostic criteria for ADHD. Recent findings from national registry data in Sweden suggests that treatment of ADHD with stimulants or atomoxetine reduces criminal offences by between 30-40%; and reduces violent re-offending on release from prison. To data there has only been one randomised control trial of methylphenidate in prisoners with ADHD, that found a very large effect with a standardised mean difference greater than 2.0. Professor Asherson has completed a pilot study of young adult prisoners and found similar large effects, and is now leading a large-scale randomised control trial to clarify how large are the medication effects compared to placebo. This work suggests that treating ADHD can lead to reductions in criminal behaviour. Independent review from prison inspectors in the UK also noted improvements in behaviour that were highly significant for some prisoners on the ADHD treatment program. Their main concern was the access to treatment and social support would be needed to maintain

these benefits on release of patients with ADHD into the community. Although there have been concerns about the potential abuse of ADHD medications in the prison environment, most cases titrated to very low doses, and did not show drug seeking behaviour. Overall the risks of abuse in prison settings appears to be low and no higher than that seen for other ADHD medications.

This symposium will start with a description of these studies of offenders with ADHD from Professor Asherson. The second speaker is Professor Barbara Franke, a leading ADHD investigator based in the Netherlands. Barbara leads the Aggressotype project, a large consortium funded by the European Union to investigate the genetic and neuropathological aetiology of aggression, and the development of novel drug and non-drug treatments such as neurofeedback. The third speaker, Jeff Stein, is a public defender who says that almost all the people he works with have a history of ADHD plus oppositional defiant disorder. He will give his perspective as someone involved in the legal profession.

This symposium will discuss the association of ADHD to criminal behaviour, the delivery of medication treatment in prison settings, and the effects of treatment, and consider the impact of ADHD from a legal perspective. We aim for an interactive discussion with the audience that will highlight the importance of diagnosing and treating ADHD among offenders.

Learning Objectives:

- That 20-30% of prisoners meet criteria for ADHD.
- That treatment of ADHD leads to reductions in criminal behavior.
- That treatments for ADHD can be delivered safely in prison settings.
- The impact of ADHD in the legal system.

Participants:

Philip Asherson, Kings College London

Barbara Franke, Radboud University Medical Center

Steven Pliszka, UT Health Science Center at San Antonio

Jeffrey Stein, Public Defender Service for the District of Columbia (PDS)

Concurrent Symposia and Workshop Sessions

2:30 PM - 4:30 PM

10. EMERGING EVIDENCE FOR THE EFFECTIVENESS OF ADHD COACHING

Chair: Jodi Sleeper-Triplett, JST Coaching & Training

Overall Abstract: ADHD coaching, which emerged in the 1990s, is a nonclinical behavioral modality that can complement the work of clinicians to improve the performance and well-being of individuals with ADHD across the lifespan.

Coaching is a client-centered wellness model predicated on the view that those coached are creative, resourceful, and whole (Sleeper-Triplett, 2010). In contrast to academic services such as tutoring or learning-strategy instruction, coaching does not prescribe the same set of steps to all participants (e.g., Allsopp, Minskoff, & Bolt, 2005). Instead, coaches are trained to use Socratic questioning and active listening to prompt awareness, reflection, and planning. This

process facilitates a client's ability to clarify personal goals and create realistic plans for achieving them, fostering self-determination.

As with health and wellness coaching, ADHD coaching typically incorporates elements of life coaching, skills coaching, and psychoeducation (Wright, 2014). It draws on current knowledge of the deficits associated with ADHD to inform the coaching relationship co-developed by client and coach (Sleeper-Triplett, 2010). By design, coaching provides a high level of structure and accountability to (a) assist in goal identification, (b) foster behavioral change and goal attainment, (c) promote improvements in functional arenas, and (d) reinforce the maintenance of gains, including those made in other therapeutic modalities. As such, ADHD coaching is increasingly recognized in the clinical literature as a useful and important component of multimodal treatment (e.g., Barkley, 2015; Kooij et al., 2010; Prevatt & Levrini, 2015; Ramsay, 2010).

This data-driven presentation will provide an overview of ADHD coaching, propose how coaching fits within a multimodal treatment approach, demonstrate the process of ADHD coaching, and provide a descriptive review of extant research (Ahmann et al., 2017; Ahmann et al., in press; Tuttle et al., 2016). A review of the literature to date suggests that ADHD coaching may hold promise in improving functional outcomes and quality of life across the lifespan and contribute positively to multimodal treatment approach.

Learning Objectives:

- Describe three or more aspects of the ADHD coaching process.
- Identify several client outcomes supported by ADHD coaching research.
- Draw conclusions about the potential value of ADHD coaching in multimodal treatment approaches.

Participants:

Elizabeth Ahmann, Maryland University of Integrative Health

Jodi Sleeper-Triplett, JST Coaching & Training

Lisa Tuttle, University of Pennsylvania

11. NEW PERSPECTIVES ON ADHD AND MOOD DYSREGULATION

Chair: Andrew Nierenberg, Massachusetts General Hospital

Overall Abstract: While problems with emotional control are not a defining feature of ADHD, they occur in a large number of individuals with ADHD and are frequently associated with a high degree of impairment. Consistent with these clinical findings, studies of underlying neurobiological mechanisms in ADHD point to abnormalities of motivation and emotional regulation, and not just attention and inhibitory control. Yet, it is unknown whether the neural underpinnings of emotional lability in ADHD are unique to ADHD or reflect common features seen across a multiplicity of diagnostic entities. This symposium will examine the nature of

emotional dysregulation in youth and adults with ADHD and other disorders, and describe the clinical and neurobiological features which characterize affected individuals.

Learning Objectives:

- Attendees will appreciate the nature of emotional dysregulation in youth with ADHD and learn how the clinical features of emotional dysregulation in youth and adults with ADHD are similar to or different from the characteristics of emotional dysregulation in other disorders.
- Attendees will appreciate the neurobiological mechanisms underlying emotional dysregulation in youth and adults with ADHD and other disorders.

11.1 AN OVERVIEW OF EMOTIONAL DYSREGULATION IN ADHD

Anthony Rostain, University of Pennsylvania, Perelman School of Medicine

Abstract: It has long been noted that significant numbers of individuals with ADHD experience difficulties with emotion regulation. Estimates of emotional dysregulation in children range from 30-40% with higher rates (32-90%) seen in adults. Although difficulties with emotional control are not a hallmark feature of DSM criteria for ADHD, they are highly associated with and often predictive of impairment throughout the lifespan, and they present a host of challenges to patients, families and care providers. They also raise interesting questions regarding the underlying neurobiology of ADHD, the putative determinants of disease progression and the mechanisms by which comorbidities such as anxiety and mood disorders emerge in this population. This talk will discuss what is known about the prevalence of emotional dysregulation (ED) in ADHD patients, conceptual and measurement issues involved in defining ED, considerations of the pathophysiology of ED (including the distinction between emotion regulation and emotion generation), the impact of ED on ADHD natural history, the links between ED and psychiatric comorbidity in ADHD patients, and the effects of ADHD treatments on ED. It will set the stage for the remaining talks in this plenary session by emphasizing the central importance of ED in ADHD as a subject for further translational and clinical research.

11.2 DEFICIENT EMOTIONAL SELF REGULATION IN THE CONTEXT OF ADHD

Joseph Biederman, Massachusetts General Hospital

Abstract: Deficient emotional self-regulation (DESR) refers to deficits in regulating emotions, difficulties stopping inappropriate behavior in response to strong emotions, and problems handling strong emotions. It manifests itself in individuals as low frustration tolerance, impatience, and quickness to anger, as well as being easily excited in response to emotional reactions. DESR is distinct from a mood disorder and differs from the persistent and severe aggressive irritability often seen in bipolar disorder. Unlike DESR, mood disorders are defined by abnormal mood and not its regulation. The difference between DESR and mood instability of bipolar disorder is of particular importance given that these two disorders respond to different pharmacologic treatments. To further characterize DESR in adults with ADHD, we analyzed data from a large study of adults with and without ADHD. Subjects were 206 adults with ADHD and 123 adults without ADHD from a family study of ADHD. They were assessed for emotional impulsivity psychiatric comorbidity, quality of Life, and psychosocial functioning. We found that 61% of our sample of adults with ADHD had DESR and its presence was associated with significant adverse effect on quality of life. In conclusion, our

study found that DESR in adults with ADHD is very common and it is associated with lower quality of life and worse social functioning, including elevated rates of traffic accidents and arrests, suggesting that DESR is an important aspect of the clinical picture of ADHD that is important to identify and remedy. The differential diagnosis between mood disorders and DESR has received very little attention in the clinical and scientific literature. This presentation will provide details on how to differentiate these two very distinct clinical entities.

11.3 AFFECTIVE CIRCUITRY AND ADHD

Jonathan Posner, Columbia University

Abstract: Although ADHD is typically considered a disorder of cognition, mood symptoms play a large role and are often quite impairing. Accumulating data suggest that neural substrate related to motivation and emotional regulation are abnormal in children with ADHD. Recent studies even point to a role of psychostimulants in normalizing these neural systems. In this presentation, we will review the neurobiology of ADHD, focusing on the role of motivation, emotional regulation, and related neural substrates.

11.4 EMOTIONAL LABILITY IN ADHD

Argyris Stringaris, National Institute of Mental Health

Abstract Emotional lability has long been recognized as a major source of impairment in youth with ADHD. Yet, it remains unclear whether the aetiology of emotional lability in ADHD is unique to this disorder or part of a trans-diagnostic dimension.
I will present a review of studies dealing with EL in ADHD and show etiologically informative data from longitudinal, twin-genetic and treatment studies.

Poster Session with Lunch

12:30 PM - 2:30 PM

Exhibit Hall C

*Denotes presenting author.

**Denotes a Data Blitz presentation.

1. DIAGNOSIS AND TREATMENT OPTIONS FOR PRESCHOOLERS WITH ADHD

Sharon Wigal[1], Phillip Chappell[2], Shannon Lubaczewski[2], Sara Ramaker[2], Richat Abbas[2], Donna Palumbo*[2]

[1]AVIDA Inc., [2]Pfizer Inc

Background: The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) classifies attention deficit hyperactivity disorder (ADHD) as a neurodevelopmental disorder, with symptoms becoming apparent as early as the preschool years. Early recognition can lead to interventions such as parent/teacher-administered behavior therapy, the recommended first-line treatment for preschool patients. There are few data, however, to inform the use of second-line, pharmacotherapy options in this population, and the use of ADHD medications in preschool patients has recently come under US Food and Drug Administration scrutiny. Here we review recent literature on the diagnosis and treatment of ADHD in preschool children.
Methods: PubMed and clinicaltrials.gov searches were conducted for trials assessing efficacy or safety of ADHD medications in children under 6 years of age. Diagnostic methods and criteria focusing on recognition of ADHD in preschool children were also surveyed.
Results: The DSM-5 describes different manifestations of ADHD in preschool vs school-aged children, but does not list separate criteria by age group. Importantly, behaviors indicative of ADHD in older children may be developmentally appropriate in preschool children. Several behavioral rating scales have been validated in children younger than 6 years of age for the assessment of ADHD. The Preschool ADHD Treatment Study (PATS) has provided the most extensive efficacy and safety data on methylphenidate (MPH) for ADHD in preschoolers to date, with significant improvement in ADHD symptoms observed with MPH compared with placebo, although adverse event-related discontinuation was higher in PATS compared with studies of MPH for ADHD in school-aged children. Since PATS was conducted, few studies designed to assess ADHD medication effectiveness in preschool children have been published. One paper reported significant improvement in ADHD symptoms with MPH formulations vs placebo, 2 studies showed no difference between MPH and risperidone or MPH plus risperidone in relief of ADHD symptoms, and 1 demonstrated the efficacy of atomoxetine vs placebo for ADHD symptoms in preschoolers. Several additional phase 2 to 4 clinical trials of ADHD medications in preschool children are listed on Clinicaltrials.gov, including placebo-controlled trials of MPH, amphetamine, clonidine, and atomoxetine.
Conclusions: The lack of data describing pharmacotherapy options for preschool children with ADHD represents an unmet need for which more research is needed.

2. BARRIERS TO EVIDENCE-BASED ADHD CARE FOR PARENTS OF AT-RISK CHILDREN

Tamara Abu-Ramadan*[1], Lea Taylor[1], Yelim Chung[1], Avery Albert[1], Kevin Antshel[1]

[1]Syracuse University

Background: ADHD is a prevalent neurodevelopmental disorder associated with negative outcomes in various domains. Though the onset of ADHD occurs during childhood or early adolescence, the average delay to evidence-based treatment is substantial. Stigma surrounding ADHD, along with parenting self-efficacy, parent's satisfaction with treatment providers, and ADHD symptom recognition/knowledge have been previously found to be associated with whether a parent will seek information about ADHD and its evidence-based treatments. The current study aimed to examine information-seeking behavior in non-treatment seeking parents of children with elevated ADHD symptoms (i.e., "at-risk") and those without elevated ADHD symptoms (i.e., "not at-risk").

Methods: Data was collected from 169 non-treatment-seeking (i.e., did not have a child diagnosed with ADHD) parents from a summer camp and Amazon's Mechanical Turk. Data collection included measurement of the parent's perception of their child's ADHD symptoms, their satisfaction with previous treatment providers, recognition of ADHD symptoms, and their perceptions of stigma towards ADHD. ADHD treatment attitudes and information-seeking behavior were also measured.

Results: A child was classified as "at-risk" if their parents rated them as above the 85th percentile for inattention or impulsivity/hyperactivity. Approximately half of the parents reported ADHD symptoms in their children that were in the at-risk level (N = 87). Between subjects ANOVA suggested that parents of children in the at-risk group were more insightful into the need for treatment, had poorer self-perception and patient-doctor relationships, and were more susceptible to perceived ADHD stigma (all ps<.01). However, there were no differences in willingness to seek information about ADHD and its treatments. Linear regressions revealed that, for parents of at-risk children, misunderstanding of ADHD was associated with more worries about treatment, satisfaction with providers was associated with fewer worries about treatment, and knowledge about ADHD was associated with fewer worries about ADHD treatment (all ps<.05). Logistic regression revealed that satisfaction with past providers was associated with desire for more information about local ADHD providers (p<.01).

Conclusions: Parents of at-risk children demonstrated worse self-perception and worse perceived patient-doctor relationships. They also were more susceptible to perceived ADHD stigma, highlighting the heightened barriers present in parents of at-risk children, compared to their peers who did not have children with elevated ADHD symptoms. In these at-risk parents, parental knowledge and understanding of ADHD symptoms, along with satisfaction with providers were predictors of parents having fewer worries about treatment. Further, satisfaction with past providers was associated with parents' information-seeking behavior. These results highlight two important avenues for reducing barriers to treatment: increasing knowledge about ADHD and treatment and improving the patient-doctor relationship, informing future interventions. In order to reduce barriers to treatments, future research should consider additional motivating factors of information-seeking behavior.

3. MULTIMODAL PSYCHIATRIST-COACH INTERVENTION FOR ADHD: CASE REPORT USING CARE GUIDELINES

Elizabeth Ahmann*[1], Katherine Smith[1], Laurie Ellington[1], Rebecca O. Pille[1]

[1]Maryland University of Integrative Health

Background: Stimulant medications are the most common treatment for Attention Deficit Hyperactivity Disorder (ADHD). However, a multimodal approach including ADHD-focused health and wellness coaching yielded improved outcomes for a young adult female struggling with graduate studies. The purpose of this case report is to illustrate the value of combining health and wellness coaching, a science-based, client-centered behavioral intervention, with psychiatric care in realizing improved ADHD management.
Methods: Using the CARE guidelines (http://www.care-statement.org/about), this case report was based on a systematic review of data collected from the point of care with a health and wellness coach collaborating with a psychiatrist in support of a client with ADHD. The client was on academic probation in a graduate-level academic program, struggling due to poorly managed ADHD.

This case report describes client improvements in ADHD management generated over a 6-week psychiatrist-health and wellness coach collaboration. The coaching interventions, also described, included use of a variety of coaching instruments, skills and strategies that will be outlined, to support the client in achieving the organizational and life skills that allowed her to resume graduate school. This is the first case report describing collaboration between a psychiatrist and a health and wellness coach in managing ADHD.

Results: Six weeks of collaboration between a psychiatrist and ADHD-focused health and wellness coach resulted in meaningful improvements for the client, in areas including academic achievement, personal growth, self-efficacy, daily functioning, organizational skills, inter-personal skills, and self-care. At the end of six weeks, the psychiatrist submitted a letter outlining these improvements to the client's academic program, and the client was allowed to resume her graduate studies. This was the most important outcome from the client's point of view. Follow-up conversations between the coach and client indicated that she maintained her gains over a several month period.
Conclusions: Multimodal intervention consisting of collaboration between a psychiatrist, health and wellness coach, and client resulted in a successful intervention for improved management of the client's ADHD and executive functioning challenges. These changes contributed to the client meeting her goal of being permitted to resume her graduate studies.

4. THE IMPACT OF POSITIVE ILLUSORY BIAS ON TREATMENT OUTCOMES AMONG ADOLESCENTS WITH ADHD

Avery Albert*[1], Lea Taylor[1], Tamara Abu-Ramadan[1], Kevin Antshel[1]

[1]Syracuse University

Background: Despite displaying significant impairments across several domains of functioning, 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). PIB appears to be primarily maladaptive in children with ADHD as it has been related to negative outcomes including aggressive behavior, poor social functioning, general maladjustment, and risky driving behavior in adolescence. Importantly, PIB has also been found to predict poor response to behavioral treatment among children with ADHD. While a few studies have examined PIB in adolescents with ADHD, this phenomenon has primarily been studied in child populations. No previous study has examined the relationship between PIB and response to treatment among adolescents with ADHD. The present study aims to address this gap in the literature by examining the impact of PIB on response to

cognitive behavioral treatment (CBT) in adolescents with ADHD. It is hypothesized that PIB will predict poor response to treatment.
Methods: Data were collected from 97 adolescents with ADHD. All participants were between the ages of 14 and 18, and were diagnosed with ADHD through a formal clinical assessment utilizing the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL), ADHD Rating Scale (ADHD-RS), as well as functional parameters. PIB was measured on a continuous scale and operationalized as the difference between participants' predicted performance and actual performance on the Gordon Diagnostic System (GDS) after completing this task. All participants completed 15 sessions of CBT over an average of 5.6 months. Outcomes of interest included parent and teacher ratings of behavioral symptoms and impairment, school tardies and absences, as well as adolescent self-reports of emotional symptoms.
Results: PIB significantly negatively predicted all CBT outcomes of interest among adolescents with ADHD. PIB significantly predicted sustained behavioral symptoms and impairment, as reported by parents and teachers at post-treatment. PIB significantly predicted emotional symptoms, as reported by adolescents at post-treatment. Finally, PIB predicted more school absences and tardies at post-treatment.
Conclusions: PIB is a clinically significant construct, as it impacts response to treatment among children and adolescents with ADHD. Findings suggest that adolescents with ADHD who display a PIB may not respond to treatment as well as adolescents who do not display this bias. Thus, PIB may be important to assess and address prior to or as part of treatment for children and adolescents with ADHD in order to increase the effectiveness of treatment and reduce the likelihood of sustained negative outcomes after treatment.

5. MULTIMODAL APPROACH FOR COLLEGE STUDENTS WITH ADHD: COMBINING EXERCISE AND ADHD COACHING

Kari Lewis*[1]

[1]ADHD Behavior Education Services, North Carolina State University

Background: It is reported that at least 25% of college students with disabilities are diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) (Journal of Attention Disorders. 2008; 13(3) 234-250) At a large east coast university it is reported that 27% of students with disabilities are diagnosed with ADHD and an additional 17% are diagnosed with ADHD plus a comorbid condition such as Learning Disability (LD) and anxiety. Students with ADHD complete a college degree less often than their non-ADHD peers. Additionally, the students with ADHD have lower GPAs, exhibit lower levels of adjustment, social skills, and self-esteem, and engage in more risky behaviors. On college campuses, typical support for students with ADHD is provided in the form of classroom accommodations, counseling interventions and less often, ADHD coaching. Although it's becoming increasingly supported in the literature that exercise affects the brain, the relationship between exercise and GPA, self-esteem and study skills in college students with ADHD has not been clearly established. The purpose of this preliminary study was to explore the effects of ADHD coaching and exercise on GPA, self-esteem, and learning study strategies in college-age students with ADHD. Additionally, the students were interviewed after the class to determine their satisfaction and the benefits they gained from the combination of exercise and ADHD coaching.
Methods: College students with a diagnosis of ADHD (n=16) were enrolled in a section of a fitness and wellness class designated only for students with ADHD. The students followed the same fitness curriculum as non-ADHD students in the same course. The ADHD-only section was extended in time by thirty minutes to include ADHD coaching which focused on the

importance of regular exercise to improve executive functioning, time management, grade monitoring and relationship issues. The students with ADHD performed the step test, the Learning Study Strategies Inventory, the Rosenberg Self-Esteem Inventory, and reported their GPA prior to and after the 16-week long course. Following the 16-week course they completed a coaching satisfaction questionnaire.

Results: Cardiorespiratory fitness, measured by the Harvard Step Test, improved and anxiety decreased. Although GPA, self esteem and LASSI scores (with the exception of anxiety) showed no improvement, students reported that the fitness/ADHD coaching class helped them improve their time management which led to positive academic and social experiences and outcomes. Students described the ADHD coaching as beneficial because they realized that they are not the only ones with ADHD and that other students with ADHD have shared experiences.

Conclusions: The fitness /ADHD coaching class helped students improve their cardiorespiratory fitness and decrease their level of anxiety. The ADHD coaching helped participants with time management and they benefited from the shared experiences of being in a class of students who all have ADHD. Given the increased risks of having ADHD, a class that combines fitness and ADHD coaching is a beneficial complement to the more conventional modes of support that exist on college campuses.

6. INVESTIGATION OF CLINICAL PRACTICE CHALLENGES IN THE MANAGEMENT OF ADHD

Greg Mattingly*[1], Rakesh Jain[2], Jani Hegarty[3], Quentin O'Brien[3]

[1]St. Charles Psychiatric Associates, [2]Texas Tech Health Sciences, [3]Health and Wellness Partners

Background: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects both children and adults. Current treatment options, while often effective, are often associated with adverse effects and/or abuse/diversion potential. The objective of this study was to characterize unmet needs in ADHD treatment for both pediatric and adult patients.

Methods: An electronic survey was sent to health care providers (HCPs) likely to treat patients with ADHD. Questions sought to characterize ADHD treatment patterns, satisfaction with currently available treatment options, clinical challenges, and unmet educational needs.

Results: 98.8% (170/172) of respondents treat patients with ADHD. 68.8% (97/141) treat both pediatric and adult populations. Respondents largely agreed that patient age plays a role in medication selection. For pediatric and adult patients, less than 40% (49/140 and 42/140, respectively) of respondents are satisfied with currently available treatment options. The most common challenges with current ADHD treatment options include breakthrough symptoms (104/135), price and access (93/135), and "crash" after medication wears off (78/135). When considering potential new treatment options, respondents would value all-day coverage (115/136), low potential for abuse/diversion (101/136), once-daily dosing (98/136), and reliable efficacy (97/136). 94.1% (127/135) of respondents believe education about current and emerging treatment options in ADHD would be beneficial to health care providers.

Conclusions: In this sample, less than 40% of respondents are satisfied with currently available ADHD treatment options. Respondents indicated a variety of common challenges with current treatments as well as desired characteristics for potential new options, suggesting a need for novel treatments for ADHD.

7. A PILOT TRIAL OF A JOINT PSYCHOSOCIAL INTERVENTION FOR BEHAVIOR AND SLEEP IN CHILDREN WITH A DISRUPTIVE BEHAVIOR DISORDER (DBD)

Sara Mills*[1], Brianna Bendixsen[2], Sue Calhoun[1], Daniel Waschbusch[1], James Waxmonsky[1]

[1]Pennsylvania State University, College of Medicine, [2]Pennsylvania State University, Harrisburg

Background: Over 50% of children with disruptive behavior disorders (DBDs) have impaired sleep (Sung, Hiscock, Sciberras & Efron, 2008), with disrupted sleep associated with worse behavioral, emotional and academic functioning comorbidity. Despite established and effective therapy treatment for behavioral and sleep problems, medication is the most common treatment for both behavioral and sleep disturbances (Meltzer, Johnson, Crosette, Ramon, & Mindell, 2010; Visser et al., 2015). Most parent management programs do not explicitly address bedtime routines, and no prior work has integrated the two to jointly target both domains. The aim of this study was to obtain preliminary data about the feasibility and acceptability of a joint intervention designed to target both pediatric behavior and sleep problems through integration of evidence based Parent Management Training (PMT) techniques.

Methods: Five families participated in the pilot study. Prior to treatment, evidence of a DBD was confirmed using the NIMH Computerized Diagnostic Interview Schedule for Children (C-DISC; Bacon 1997). Delayed SOL was defined as longer than 30 minutes to fall asleep, which was confirmed over a two-week period using both actigraphy and parent sleep log. Once enrolled, families participated in three, 60-minute therapy sessions. Parent ratings of child DBD symptoms and parenting practices were collected at baseline before and after treatments. Child sleep patterns were assessed by actigraphy and parent sleep log for one week at baseline and endpoint.

Results: All five families completed the program with 96 % attendance overall, and completed the core intervention, creation of a nighttime behavioral report card (NRC). SOL decreased from

M=51.8 (SD =14.2) to M=38.6 (SD=23.2) with large effects (ES=.93). Parent reported child ADHD symptoms decreased from M=24.8 (SD=6.22) to M=21.2 (SD=12.8) with average effects (ES=.58). There was no change in parent reported child ODD symptoms. On the Alabama Parenting Questionnaire, positive parenting scores increased from M=62.2 (SD=11.1) at baseline to M = 67.0 (SD=5.20) at endpoint (ES=.43). Bivariate correlations were computed to assess the relationship between child SOL and parenting practices with separate analyses for baseline and endpoint. There was a negative relationship between child SOL and positive parenting practices at baseline r=-.56, NS, and endpoint r = -.88, $p < .05$. However, there was no significant association between positive parenting practices scores and child SOL overtime.

Conclusions: Our preliminary findings suggest that this intervention is feasible and possibly efficacious for sleep problems as evidenced by a large decrease in child SOL. There was no change in ODD symptoms; however, our measure inquired about symptoms across the day and may have been insensitive to changes seen in the evening. We did detect a hypothesized relationship between positive parenting and SOL as the intervention emphasized use of praising and rewards for good behavior over focusing on extinguishing negative behaviors, which may be more physiological arousing. This preliminary data will aid in the development of a larger study employing the same intervention for children with DBDs and significantly delayed SOL. Limitations include a small sample size, inconsistent actigraph data collection, and reliance on

self-report data. Future studies should also consider questionnaires that ask about specific evening time behaviors.

8. GOAL ORIENTATION AND STIMULANT MISUSE IN COLLEGE STUDENTS

Lea Taylor*[1], Avery Albert[1], Tamara Abu-Ramadan[1], Kevin Antshel[1]

[1]Syracuse University

Background: Stimulant medications are an evidence-based treatment for ADHD. However, research suggests that rates of stimulant misuse (i.e., illicit use of stimulant medication without a prescription) are growing, particularly among college students. Stimulant misuse is distinct from other substance misuse in that the primary motivation is academic performance enhancement. Despite this motive, stimulant misuse is associated with factors that predict poor academic performance. Current research suggests that positive perceptions of stimulants, substance use, and procrastination predict stimulant misuse, yet is limited by relying on univariate analyses and the low variance explained. Given the goal-directed nature of stimulant misuse, there is a gap in the literature considering the effects of academic goal orientation. Previous literature has identified two goal orientations: mastery or task-oriented goals (i.e., task mastery and within-person comparisons) and performance or ego-oriented goals (i.e., outcomes and between-person comparisons). The current study aims to investigate the association between academic goal orientation and stimulant misuse, informing efforts to potentially reduce stimulant misuse. We hypothesize that (a) previous identified factors associated with stimulant misuse will be replicated, yet (b) after controlling for the impact of these factors, greater academic ego-orientation will be associated with more stimulant misuse.

Methods: We collected data from 309 students from a large private university in the northeastern United States. We examined history of stimulant misuse, academic goal orientation, ADHD symptoms, perfectionism, sensation-seeking, procrastination, stress, substance use, perceptions of stimulant misuse norms, and access to stimulant medication. Stepwise logistic regression was used; previously identified factors associated with stimulant misuse were entered simultaneously in step 1 and academic ego-orientation entered in step 2. In addition, ROC curves were examined to determine the clinical utility of these factors towards predicting stimulant misuse.

Results: Between subjects ANOVAs indicated that individuals who had misused stimulants had greater levels of academic ego-orientation, procrastinated more, perceived stimulant misuse as more normative, perceived access to stimulants, and had greater risk of other substance use than those who had not (all ps<.001). Logistic regressions revealed that access to stimulant medication and procrastination predicted stimulant misuse. After controlling for the impact of all other previously identified variables, only higher levels of academic ego-orientation were associated with stimulant misuse (R2 = .56). ROC curve analysis conducted on a combined variable of access to stimulants and academic ego-orientation indicated a good ability to predict stimulant misuse (AUC = .86).

Conclusions: Academic ego-orientation and access to stimulants are important factors in predicting stimulant misuse. This information has clear clinical utility in the development of both primary and secondary prevention programs. Primary prevention programs may focus on modifying the academic environment to promote task-oriented goals. In addition, secondary prevention programs may utilize the results of the current study to screen for students that may be at greater risk for misusing stimulants, warranting targeted intervention.

9. EVIDENCE OF POOR PATIENT ENGAGEMENT IN TREATMENT FOR ADHD: A 17-YEAR ELECTRONIC MEDICAL RECORDS DATA MINING STUDY FROM A LARGE HEALTH CARE ORGANIZATION

Ronna Fried*[1], Joseph Biederman[1], Maura Fitzgerald[2], Barbara Storch[2], Alexa Pulli[2], K. Yvonne Woodworth[2], Roy Perlis[1]

[1]Massachusetts General Hospital & Harvard Medical School, [2]Masschusetts General Hospital

Background: ADHD is a prevalent and morbid neurobiological disorder that has been associated with a wide range of adverse outcomes. Data from large datasets documents that stimulants decrease the risks for many adverse outcomes, yet compliance with stimulants remains very poor. A growing body of evidence shows that patients who engage with their health care providers have much better clinical outcomes; therefore, the rate of renewal of the first stimulant prescription in new patients initiating treatment is an important objective metric of adherence. The main aim of the present study was to evaluate objective contemporaneous rates and correlates of patient engagement in ADHD treatment.

Methods: Prescription and demographic data were extracted from the Partners HealthCare Research Patient Data Registry (RPDR) for patients younger than 17 years of age who were prescribed a CNS stimulant between January 1, 2000 and December 31, 2016. ADHD patient engagement was systematically evaluated by examining the rate of renewal for the first prescription for a stimulant medication within a 17-year period, and patient engagement was defined as having at least one initial prescription refilled. A prescription refill was defined in three ways: 1) For single initial prescriptions, patients needed to have a second prescription at any point after the date on the initial prescription; 2) For initial prescriptions post-dated 2 months, patients needed to have a third prescription >30 days after the date on the initial prescription; and 3) For initial prescriptions post-dated 3 months, patients needed to have a fourth prescription >60 days after the date on the initial prescription.

Results: The sample consisted of 2,685 patients, with an average age of 12.4 ± 3.0 years. Seventy-three percent were male, 72% were Caucasian, and 92% spoke English as their primary language. Patients came from all economic classes with 26% upper-class, 43% middle-class, and 30% lower-class. 1,573 (57%) out of 2,685 patients engaged in treatment.

Conclusions: The results of this study support the hypothesis that patient engagement in stimulant treatment for ADHD is poor. A decade of electronic medical record (EMR) data from the large health care organization shows that only 57% of close to 3,000 patients engaged in treatment. These findings provide compelling evidence for poor rates of patient engagement in stimulant treatments for ADHD and are consistent with findings reported in a recent literature review.

10. THE CLINICAL CORRELATES OF WORKING MEMORY DEFICITS IN YOUTH WITH ADHD: A COMPREHENSIVE LITERATURE REVIEW

Ronna Fried*[1], Jessica Abrams[2], James Chan[2], Anna Hall[2], Leah Feinberg[2], Amanda Pope[2], Barbara Storch[2], Stephen Faraone[3], Joseph Biederman[1]

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

Background: Working Memory (WM) is a domain of executive functioning often impaired in individuals with attention deficit/hyperactivity disorder (ADHD). While assumed to cause difficulties across functioning, the scope of impairments from WM deficits in ADHD has not

been investigated. The aim of this study was to examine outcomes associated with WM deficits in ADHD.
Methods: We conducted a search of the scientific literature on WM deficits, and Freedom from Distractibility (FFD), in ADHD using PubMed and PsycInfo databases.
Results: The final sample included 11 controlled studies of WM/FFD deficits in ADHD with operationalized assessment of outcomes in academic, social, and emotional areas. WM assessment was divided into auditory-verbal memory (AVM) and spatial-visual memory (SWM). Seven studies examined WM deficits in academic functioning, eight studies assessed WM deficits in social functioning, and three assessed WM deficits in psychopathology.
Conclusions: The majority of the literature suggests that WM deficits affect primarily academic functioning.

11. THE RELATIONSHIP AND PREDICTIVE VALUE OF CORE ADHD SYMPTOMS AND EXECUTIVE FUNCTION DEFICITS

Michael Silverstein[1], Stephen Faraone[2], Terry L. Leon[3], Thomas Spencer[4], Joseph Biederman[4], Lenard Adler*[3]

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

Background: Although executive function deficits (EFDs) are not a core part of the DSM-5 diagnostic criteria, many adults with Attention Deficit Hyperactivity Disorder (ADHD) also have significant symptoms and impairments from EFDs. Understanding the relationship between core ADHD symptoms of inattention (IA) and hyperactive-impulsivity (HI) and EFD can assist clinicians in identifying and screening their adult ADHD patients for EFDs. Additionally, examining the predictive utility of ADHD measurement instruments, such as the Adult ADHD Investigator Symptom Rating Scale (AISRS), in identifying those at risk for EFDs can further assist in patients with EFDs. The objectives of the present study are: (1) Identify the relationship between the core DSM-5 ADHD symptoms and EFD; (2) Evaluate the ADHD characteristics of those with executive dysfunction; (3) Examine the predictive utility of the AISRS in identifying those with adult ADHD and EFD.
Methods: Two patient samples were combined from a larger study to recruit patients with and without ADHD to update and validate the ASRS (Adult ADHD Self-Report Scale) v1.1 Screener for DSM-5; a referred sample of adults recruited as part of the NYU Adult ADHD Program and patients screened for ADHD at a primary care physician (PCP) practice in the New York area. The ACDS v1.2 was used to evaluate for adult ADHD and the ASRS was administered to measure symptom impairment. The AISRS was also used to measure ADHD symptom impairment for a subset of the referred patients (n= 85), and the BRIEF was also used to measure EFDs for the same subset. EFDs via the BRIEF were classified as subjects having a GEC T score ≥ 65 (one and ½ SDs above the control mean). All three of the ADHD scales utilized expanded versions which evaluate the DSM adult ADHD symptoms (IA and HI), as well as nine EFDs.
Results: 299 respondents were studied across the two samples, of which 170 had adult ADHD. ADHD symptoms as measured by the ASRS and AISRS total 18 DSM symptom scores, 9 item IA scores, & 9 item HI scores and EFD as measured by the BRIEF were highly correlated, Spearman's rho's .52-.87, $p < .001$. Of the 72 subjects with EFDs via the BRIEF, 66 had ADHD, but six did not have ADHD. ADHD symptom scores had a moderately strong correlation with EFD symptoms as measured by the AISRS, Spearman's rho's .74-.91, $p < .001$. Total 18 DSM symptom scores and IA symptom scores tended to have somewhat stronger

correlations with EFDs than HI symptom scores. Correlations remained significant when controlling for age, gender, ethnicity, and ADHD status. The subjects with clinically significant EFD as measured by the BRIEF were distributed in both IA and Combined ADHD presentations. Binary logistic regression demonstrated that ASRS and AISRS HI, IA, and total symptom scores significantly predicted EFD. ROC curve procedures also suggest that an AISRS DSM 18-item cutoff score of 28 was most predictive of EFD via BRIEF.
Conclusions: (1) ADHD symptoms as measured by self-report and clinician evaluation were strongly correlated with and were predictive of significant EFD – with both IA and HI symptoms highly correlating with EFD; (2) Increased ADHD severity increased the likelihood of having EFDs; (3) An AISRS 18-item score of 28 was predictive of BRIEF EFD; and (4) Severity of ADHD symptoms was not the full story, as six subjects were EFD+, but ADHD-; all still had subthreshold ADHD symptoms and/or co-morbidities, which may have contributed to the EFDs.

**12. DO SUBSYNDROMAL MANIFESTATIONS OF MDD IN CHILDREN AT GENETIC RISK FOR MDD PREDICT THE DEVELOPMENT OF MAJOR DEPRESSION? A FIVE-YEAR LONGITUDINAL CONTROLLED STUDY

Joseph Biederman*[1], Mai Uchida[2], Maura Fitzgerald[1], Caroline Kelberman[1], Hilary Woodworth[1], Nicholas Carrellas[1]

[1]Massachusetts General Hospital, [2]Massachusetts General Hospital & Harvard Medical School

Background: Pediatric major depressive disorder (MDD) is a prevalent and highly morbid disorder often affecting functioning in social and academic domains. Although research has shown that early intervention helps prevent development and progression of the disorder, more tools are needed to efficiently, cost-effectively, and accurately identify children and adolescents at the greatest risk for development of MDD in order to target early intervention at those who would benefit from it most. The Child Behavior Checklist (CBCL) Anxiety/Depression scale is one such potential tool.
Methods: We followed 564 children, ages 6-17, with and without subsyndromal scores on the CBCL Anxiety/Depression scale (n=81 and 483, respectively) and with and without parents with MDD (n= 293 and 271, respectively) over 5 years. We focused our analysis on the development of MDD diagnoses and psychosocial functioning among the 4 groups in the years of follow-up.
Results: Children with parents with MDD and subsyndromal scores on the CBCL Anxiety/Depression scale at baseline were twice as likely to develop MDD by the follow-up visit in adolescence than children with parents with MDD who lacked an elevated score on the CBCL Anxiety/Depression scale. This group with genetic risk and elevated CBCL Anxiety/Depression scale scores also had the highest likelihood of developing psychosocial impairments at the follow-up. Children with elevated CBCL Anxiety/Depression scores whose parents did not have MDD showed intermediate outcomes; while they were significantly less likely to develop MDD compared to children with both genetic risk and elevated CBCL Anxiety/Depression scores, they were significantly more likely to develop MDD compared to children with only genetic risk or children with neither genetic risk or elevated CBCL Anxiety/Depression scale score.
Conclusions: Our findings show that the CBCL Anxiety/Depression scale is useful in identifying children most at risk for development of MDD. Given its utility, low cost, and replicability, if implemented more widely among pediatric clinics, the CBCL

Anxiety/Depression scale should greatly assist in detection of children at the highest risk for MDD, allowing for early intervention to be targeted at those who need it most.

13. SPORT CONCUSSION AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN STUDENT ATHLETES: A COHORT STUDY

Joseph Biederman*[1], Mary Alexis Iaccarino[2], Maura Fitzgerald[1], Alexa Pulli[1], K. Yvonne Woodworth[1], Thomas J. Spencer[3], Ross Zafonte[4]

[1]Massachusetts General Hospital, [2]Spaulding Rehabilitation Hospital & MassGeneral Hospital for Children, [3]Massachusetts General Hospital & Harvard Medical School, [4]Spaulding Rehabilitation Hospital

Background: Attention deficit hyperactivity disorder (ADHD) is associated with impulsive behavior and inattention, making it a potential risk factor for sport related concussion (SRC). The objectives of this study were to determine if ADHD is an antecedent risk factor for SRC and whether it complicates recovery from SRC in youth athletes.
Methods: Student athletes with a history of SRC were evaluated to determine the presence of ADHD using diagnostic interview and whether ADHD symptoms began prior to or after SRC. Student athletes were age matched to historical controls with ADHD. Concussion specific measures of concussive symptoms and cognitive function were compared in student athletes with SRC with (SRC+ADHD) and without (SRC) ADHD.
Results: ADHD was significantly overrepresented in youth with SRC compared to controls (35% vs. 14%; $\chi 2=7.65$, $p=0.006$). The age at onset of ADHD was always earlier than the age at time of SRC (6.1 ± 3.0 years of age vs. 15.5 ± 2.6 years of age; $t22=-11.25$, $p<0.001$). Student athletes with SRC and ADHD reported more concussive symptoms compared to athletes without ADHD and were more likely to have a history of greater than one concussion.
Conclusions: The results of this study support our hypothesis that ADHD is an antecedent risk factor for SRC and may contribute to a more complicated course of recovery from SRC. Providers that care for youth athletes with ADHD should be aware of the vulnerabilities of student athletes with ADHD toward SRC and its complications.

14. OPEN BOARD

15. PARENTAL STIGMA ABOUT MEDICAL AND MENTAL HEALTH ISSUES: AN INVESTIGATION INTO THE DIFFERENTIAL EFFECTS OF PARENT GENDER AND STIGMA ON ADHD VS. ASTHMA

Yelim Chung*[1], Tamara Abu-Ramadan[1], Lea Taylor[1], Kevin Antshel[1]

[1]Syracuse University

Background: As children are dependent on their parents to make healthcare decisions, parents are gatekeepers to the potential evaluation and treatment of various health conditions. Parental perceptions and experiences of stigma may affect parental choices and behaviors to pursue or not pursue treatment for a health condition. Despite the large stigma literature, there remains a need to understand how stigma may affect parental decisions about accessing evidence-based ADHD treatments. Moreover, few studies have considered how stigma may differentially affect mothers and fathers and which specific types of stigma may play a role in parents' perceptions of mental health conditions (e.g., ADHD) compared to physical health conditions (e.g., asthma). The following hypotheses were tested: a) Stigma towards ADHD will be higher

than stigma for asthma, except for ratings of perceived coercion for treatment; b) Fathers will have a higher global level of stigma about ADHD than mothers, and c) Fathers have a greater belief that the child or the child's parents are at fault for their behavior. This study will seek to highlight the different types of stigma that may play a role in mother and father perceptions of physical and mental health conditions. Results will also provide an overall outlook on common parent concerns and ideologies about ADHD.

Methods: Data was collected from 63 parents with children from a non-ADHD-treatment-seeking population. Parents participated in an online study that assessed perceived stigma towards individuals with medical and mental health disorders. Vignettes with precedence in the child stigma literature were used to assess parents' general perceptions about ADHD and asthma, attitudes towards symptoms that warranted medical treatment, and ability to correctly label symptoms. Repeated measures, between-subjects, and factorial ANOVAs were used for hypothesis testing.

Results: Significant differences in stigma emerged across ADHD and asthma for both genders ($ps<.05$). Both fathers and mothers rated children with ADHD as more dangerous and expressed an increased desire to avoid children with ADHD. Both fathers and mothers endorsed higher perceived coercion for treatment for children with asthma. Further, both fathers and mothers reported that a child with ADHD was more to blame for their condition than a child with asthma. These results suggest that parental stigma may be greater for mental health disorders such as ADHD than for a medical illness like asthma. Contrary to our hypothesis regarding contrasting mother/father perceptions, our findings supported that mothers and fathers did not significantly differ on attributions for the cause of different illnesses.

Conclusions: Non-ADHD-treatment-seeking mothers and fathers are equally likely to attribute ADHD to child-related factors (e.g., effort). Mothers and fathers both endorsed greater levels of stigma towards ADHD than for asthma. As parents serve as the gatekeeper to their children's health, future research may aim to develop interventions to decrease these specific types of stigma towards ADHD, hopefully decreasing barriers to treatment. Additional work should be done to replicate these findings and expand on possible differences in father-mother perceptions of ADHD.

16. THE IMPACT OF ADHD IN THE CANADIAN WORKPLACE

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

[1]START Clinic for Mood and Anxiety Disorders

Background: Attention Deficit Hyperactivity Disorder (ADHD), though previously considered to be a pediatric disorder, has gained increased attention worldwide with the literature suggesting that it can persist into adulthood for up to 65% of those first identified in a pediatric population (Barkley et al., 2002; Kessler et al., 2005). Untreated adult ADHD can lead to multiple impairments in one's life including behavioural and conduct problems, cognitive difficulties, and impaired psychosocial functioning. Pervasive ADHD is associated with higher rates of comorbid psychiatric conditions. Our research focused on obtaining information from individuals both with ADHD and without a diagnosis with respect to their experience in workplace settings.

Methods: Individuals with a diagnosis of ADHD (N=100) were asked to complete an online survey with questions assessing demographic factors, employment history, attentional symptoms, and their overall assessment of their quality of life. This sample was compared to a gender-matched group of healthy controls (N=500) that completed a similar questionnaire.

Results: Individuals with a diagnosis of ADHD were significantly more impaired with respect to their educational and employment outcomes. For example, those with ADHD had on average lower levels of education and often reported that their symptoms prevented them from pursuing their ideal career. In fact, only 3% of those with ADHD obtained a graduate or post-graduate degree, compared to 10% of the control group. As well, in terms of current employment, only 53% of individuals with ADHD were currently employed, compared to 100% of the control group. Individuals with ADHD were more prone to have changed jobs more frequently compared to controls ($p<0.05$) and had on average much lower incomes. The impact of ADHD in the workplace was also examined in terms of perceived stigma, personal coping mechanisms and impact of a workplace medical benefits plan.
Conclusions: These results demonstrate that it is essential to recognize the impact of an ADHD diagnosis on overall workplace productivity, the individual's view of themselves, psychological wellbeing, maturity, educational achievements, interpersonal relationships and life outcomes.

17. REWARD-BASED LEARNING AND THE SEVERITY OF SUBSTANCE ABUSE RISK IN DRUG-NAIVE YOUTH

Iliyan Ivanov*[1], Muhammad Parvaz[2], Kristen Kim[3], Jeffrey Newcorn[2]

[1]Mt. Sinai NYC, [2]Icahn School of Medicine at Mount Sinai, [3]Rutgers University

Background: Computational methods have been used to detect differences in behavior on neurocognitive tasks among individuals with mental disorders, including those diagnosed with ADHD, vs. unaffected counterparts. We conducted a proof of concept study comparing results obtained from conventional behavioral analyses of task performance (e.g., reaction time) with computational analyses (e.g. prediction error, congruency, and learning rate) calculated from different task conditions in a hybrid Anticipation, Conflict, Reward (ACR) task. The task includes reward cues, outcomes and conflict resolution components. The objective was to examine whether computational variables better differentiate groups of drug naïve youth with varying levels of risk for later substance use disorders (SUD).
Methods: We recruited 41 drug-naïve youth (31 males, 10 females) ages 8-13 years old (mean = 10.00, SD = 1.57) divided into 3 groups: Healthy Controls (HC, n=13), including participants with neither ADHD nor parental SUD, Low Risk (LR, n=12), including participants with ADHD only, and High Risk (HR, n=15), including participants with both ADHD and parental SUD. Reaction times (RT), which assesses speed of motor responses to targets as a function of reward cue and target congruency, were analyzed using a 2 (Reward: Reward, No-reward) × 2 (Congruence: Congruent, Incongruent) × 3 (Group: HC, LR, HR) mixed Analysis of Variance (ANOVA). Applying simple reinforcement learning models, we also computed variables such as learning rates, prediction t-score, and congruence t-score, that were analyzed via a multivariate analysis of variance (ANOVA) with Group (Control, LR, HR) as a fixed factor. Both linear and polynomial contrasts were evaluated and post hoc pair-wise group comparisons were conducted.
Results: The 2 mixed ANOVA for RT revealed a significant main effect of Reward [$F(1,37)=26.0, p<.001$] and Congruence [$F(1,37)=141.2, p<.001$] but no Group main effect. The multivariate ANOVA showed significant linear effects in learning rate (Contrast Estimate = 0.181, $p=.038$), and in the congruence-t score (Contrast Estimate=1.16, $p=.017$). Post-hoc comparisons revealed that these effects were driven by the differences between HC and HR adolescents (learning rate: $p=.038$, HR>HC; congruence: $p=.017$, HR>HC).
Conclusions: The findings from this proof of concept study highlight the deficits in learning seenas a function of congruence in ADHD adolescents at HR for SUD. These findings also

demonstrate the utility of computational analyses, which can offer added value over conventionalbehavioral analyses in more precisely distinguishing group differences in relation to SUD risk.

18. SLUGGISH COGNITIVE TEMPO PREDICTS ACADEMIC FLUENCY IN CLINICALLY-REFERRED YOUTH, BEYOND CONTRIBUTIONS OF CORE SKILLS, INATTENTION, AND GRAPHOMOTOR SPEED

Lisa Jacobson*[1], Mark Mahone[2]

[1]Johns Hopkins School of Medicine, Kennedy Krieger Institute, [2]Kennedy Krieger Institute

Background: Sluggish Cognitive Tempo (SCT) comprises a distinct behavioral phenotype that appears to partially overlap with Attention-deficit/Hyperactivity Disorder (ADHD) and other disorders. SCT is characterized by such symptoms as being slow to complete tasks, easily confused, or mentally foggy; appearing drowsy, sleepy, or frequently lost in thought; and/or lacking initiative. Factor analytic work has revealed sleepy-sluggish, low initiation, and daydreamy sub-components of SCT, with each differentially associated with ADHD inattention symptoms. Much of the work in this area has examined associations between caregiver ratings of children's SCT symptoms and caregiver ratings of performance or behavioral symptoms; few studies have examined actual child performance to determine whether reported SCT is predictive of slowed speed of performance on timed tasks.
Methods: We examined timed and untimed reading (standardized measures of single word reading, reading fluency) and math (standardized measures of math calculation, math fluency) skills in 247 clinically-referred youth (Mean age=11.6, SD=2.8, range=6.9-20.4; 67.6% male), for whom parents provided ratings of SCT and ADHD symptoms. A series of hierarchical regressions were used to predict timed academic fluency from SCT ratings, controlling for the untimed skill and inattention symptom severity; an additional step included a proxy for graphomotor speed (Wechsler Coding score) as a predictor.
Results: Results indicated that SCT consistently predicted timed academic fluency, above and beyond inattention and graphomotor speed. Specifically, SCT symptoms accounted for a small but significant amount of additional variance (SCT $\Delta R2=.037$, $p=.001$; total model $R2=.466$) in reading fluency performance, after controlling for untimed word reading ability ($R2=.429$, $p<.001$) and inattention symptom severity ($\Delta R2=.000$); the SCT Low Initiation ($\beta=-.263$, $p=.001$) and Sleepy-Sluggish ($\beta=.138$, $p=.011$) components contributed significantly to prediction of reading fluency. When word reading, inattention, and graphomotor speed were included in the model (total model $R2=.580$), all three SCT subscales (SCT $\Delta R2=.032$, $p=.001$; Low Initiation $\beta=-.168$, $p=.021$; Sleepy-Sluggish $\beta=.176$, $p<.001$; Daydreamy $\beta=-.122$, $p=.025$) predicted reading fluency.

Similarly, SCT symptoms added significantly to prediction of math fluency ($\Delta R2=.034$, $p=.004$), over and above untimed math ability ($R2=.352$, $p<.001$) and inattention severity ($\Delta R2=.009$, $p=.064$); the SCT Sleepy-Sluggish ($\beta=.152$, $p=.008$) and Daydreamy ($\beta=-.175$, $p=.007$) components were most strongly predictive of math fluency. When untimed calculation skills, inattention, and graphomotor speed were included in the model (total model $R2=.512$), SCT remained a small but significant predictor of math fluency (SCT $\Delta R2=.039$, $p<.001$; Sleepy-Sluggish $\beta=.188$, $p<.001$; Daydreamy $\beta=-.188$, $p=.001$).

Conclusions: Taken together, results move the field beyond reliance upon method variance and provide initial evidence that aspects of caregiver reported SCT uniquely predict timed

measures of child performance, beyond contributions of core academic skills, inattention, and motor speed.

19. THE SOCIAL CONTEXT OF ALCOHOL USE AMONG YOUNG ADULTS WITH ADHD HISTORIES

Traci Kennedy*[1], Christine Walther[2], Sarah Pedersen[1], Kirsten McKone[1], Elizabeth Gnagy[3], William Pelham[3], Brooke Molina[1]

[1]University of Pittsburgh, [2]University of Houston, Clear Lake, [3]Florida International University

Background: Perceived peer substance use strongly predicts adolescents' alcohol use – especially among adolescents with a history of ADHD (Marshal et al., 2003; Belendiuk et al., 2016). However, the extent to which these associations continue into adulthood among individuals with childhood ADHD is unknown. The present study examined the relation between peer substance use and adults' own alcohol use longitudinally across a broad age range (early adulthood to age 29) and compared these associations for those with versus without ADHD histories. We hypothesized stronger relations for adults with ADHD histories.
Methods: As part of the Pittsburgh ADHD Longitudinal Study, 443 individuals (248 ADHD, 195 nonADHD; 88.9% male; 81.9% White) completed measures of perceived substance use by their friends (i.e., alcohol, marijuana, and other drugs), their own alcohol use (past 12-month frequencies of drinking alcohol, binge drinking, and drunkenness), and demographic information (e.g., gender, SES, marital status, college enrollment) approximately biannually at ages 18-29.
Results: Controlling for baseline demographics and age 21 alcohol use, hierarchical OLS regressions revealed that peer substance use at age 21 was related to past-year frequency of drinking alcohol ($B = .16$, $p < .01$), binge drinking ($B = .30$, $p < .001$), and drunkenness ($B = .34$, $p < .001$) at age 22. Moreover, peer use at age 21 continued to relate positively to frequency of binge drinking ($B = .20$, $p < .01$) and drunkenness ($B = .29$, $p < .001$) at age 29. There were no significant moderating effects of ADHD history at either age. A latent growth curve model of peer substance use from age 18-29 suggested a piecewise linear pattern for both ADHD and nonADHD groups, increasing to age 21 then remaining stable to age 29 ($SB\chi^2 = 108.75$, $p = .002$; CFI = .946; RMSEA = .031; SRMR = .097).
Conclusions: Peer substance use is a long-lasting factor in young adults' alcohol use, both for those with and without ADHD. Correlated growth between perceived peer use and one's own alcohol use as a function of ADHD history will also be examined; declines in peer drinking after age 21 may differentially relate to alcohol use by older individuals with versus without ADHD.

Peer contexts remain influential in alcohol use through young adulthood. Interventions to reduce high-risk drinking should target interactions with substance-using peers.

20. YOUNG ADULT OUTCOMES AS A FUNCTION OF ADOLESCENT ADHD SYMPTOM TRAJECTORIES: INATTENTION, HYPERACTIVITY/IMPULSIVITY, AND OPPOSITIONAL BEHAVIOR

Traci Kennedy*[1], Christine Walther[2], Sarah Pedersen[1], Kirsten McKone[1], Elizabeth Gnagy[3], William Pelham[3], Brooke Molina[1]

[1]University of Pittsburgh, [2]University of Houston, Clear Lake, [3]Florida International University

Background: Adolescent attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity/impulsivity, and – for many – oppositional behavior. By young adulthood, symptoms of hyperactivity/impulsivity tend to decrease, whereas symptoms of inattention remain relatively stable (Caye et al., 2016). However, the relations among these three symptom trajectories as they progress across adolescence has not been delineated. Moreover, despite these average trends in symptom change over time, there is substantial variability among individuals with ADHD in the progression of symptoms across these three domains. Group-based trajectory modeling, a person-based approach, accounts for such variability by approximating subgroups of individuals who share similar patterns of a behavior across time (Nagin, 2005). This study sought to characterize overlaps in symptom progression across the domains of inattention, hyperactivity/impulsivity, and oppositional behaviors among adolescents with ADHD by modeling these three trajectories jointly.

Methods: As part of the Pittsburgh ADHD Longitudinal Study, 270 individuals diagnosed with ADHD in childhood completed the Disruptive Behavior Disorders Rating Scale at ages 13-18. All participants took part in a summer treatment program, which included intensive behavioral and parenting interventions (Molina et al., 2016).

Results: Using group-based trajectory modeling, we first modeled each symptom trajectory across ages 13-18 separately. Based on BIC and AIC, a 5-group solution provided the best fit to the data. After determining the optimal functional forms of the trajectories for each group, we then modeled the three symptom trajectories jointly. Five groups across the three trajectories yielded adequate posterior probabilities of group membership, ranging from .62 to .88.

The largest group (31% of the sample) comprised individuals whose symptoms tended to begin low at age 13 and decline by age 18, across all three symptom domains (ps <.05-.001). Similarly, all symptom trajectories declined in group 3 (21%), but began and finished at higher levels (ps <.05-.001). Group 4 (23%) was characterized by declines in hyperactivity/impulsivity and inattention symptoms, but increasing oppositional behavior, perhaps reflecting a subgroup of individuals at risk for adult antisocial behavior despite decreases in ADHD core symptoms (ps <.05-.001). Some individuals (group 2; 19%) tended to experience relative stability in hyperactivity/impulsivity and oppositional symptoms across time, alongside increasing inattention (ps <.05-.001). Lastly, a small subset (group 5; 7%) experienced the highest levels of all symptoms, which declined by age 18 for hyperactivity/impulsivity and inattention, but increased for oppositional behavior (ps <.05-.001). Descriptive analyses suggest that individuals in groups 1 and 2 (low declining and low stable across all three symptom domains) tended to be more socioeconomically advantaged; groups did not differ by sex.

Conclusions: These findings highlight the substantial variability in ADHD symptom trajectories across adolescence that may deviate from typical, average-level trends. Moreover, although some subgroups of adolescents with ADHD experience commensurate declines in symptoms across domains, others experience more nuanced patterns. Analyses will additionally predict key outcomes in adulthood, including functional impairment and substance use, as a function of symptom trajectory group.

21. IS SCTA RISK FACTOR FOR INTERNALIZING PSYCHOPATHOLOGY?

Keith McBurnett*[1], Shaikh Ahmahdh[1], Lauren Friedman[1], Miguel Villodas[2], Linda Pfiffner[1]

[1]University of California, San Francisco, [2]San Diego State University

Background: Internalizing disorders are the most prevalent diagnoses in adulthood(Ansseau et al., 2004) have massive impact on quality of life.(Rapaport, Clary, Fayyad, & Endicott, 2005) They appear to be rising in incidence, and impairment associated with internalizing disorders increased 15-20% from 2005 to 2015.("Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015," 2016)

Sluggish Cognitive Tempo (SCT) is a hypothesized dimension of psychopathology characterized by inconsistent alertness and orientation, and manifested by symptoms of sluggishness, apparent drowsiness, and apparent daydreaming.(K. McBurnett & Pfiffner, 1999) The evidence for association of SCT with internalizing disorders is robust with respect to inclusion of I and HI in statistical models.(Becker et al., 2016) This is a critical hint that SCT may be an independent risk factor for future development of internalizing psychopathology.

We speculate that children with SCT become increasingly aware that they are not prepared to quickly answer questions, remember names of acquaintances, or participate in the rapid colloquial exchanges among schoolmates. The inevitable embarrassments resulting from these social failures become learned associations, resulting in avoidance and exacerbation of anticipatory anxiety. Withdrawal and peer neglect/exclusion (social isolation), even on the margins, add to the net lack of buffers and social learning.

Methods: We examined the predictive validity of baseline SCT using the baseline and 9-11 month follow-up data from an RCT of psychosocial trial for children with ADHD, Predominantly Inattentive presentation. Subjects were 165 children in grades 2–5 (mean age = 8.66 years, range 7–11).

Measures included parent- and teacher-rated child psychopathology (Child Symptom Inventory) and parent-rated child internalizing psychopathology (Child Depression Inventory, and internalizing subscale from the Social Skills Improvement System).

Results: Both models (CDI and SSIS) were significant, with overall model variances of 20% and 17%, respectively. After accounting for baseline IA, HI, and covariates, baseline SCT symptoms uniquely contributed a significant amount of variance to parent-reported symptoms of depression at follow-up ($\Delta R2 = .041$, $p = .010$). The unique contribution of baseline IA symptom severity was smaller: $\Delta R2 = .026$, $p = .037$). Baseline HI was not a significant predictor of depression at follow-up. Baseline SCT symptoms also uniquely predicted parent-reported internalizing symptoms on the SSIS at follow-up ($\Delta R2 = .093$, $p < .010$), whereas neither IA nor HI symptoms were significant predictors.

Conclusions: Severity of SCT may be a risk factor for developinginternalizing psychopathology. These findings are exploratory and must be interpreted with caution, particularly in view of the lack of similar findings in child- and teacher-reported internalizing problems (not reported). If these findings prove replicable, they would support an entirely new avenue for prevention. Emerging treatments for SCT,(Pfiffner et al., 2007)(Keith McBurnett et al., 2017) while similar in some respects to ADHD treatments, bear little resemblance to current treatments for anxiety or depression and therefore may be unforeseen preventative resources.

22. PREVALENCE AND IMPACT OF UNDER- OR MISDIAGNOSED ADHD IN ADULTS REFERRED FOR THE TREATMENT OF MOOD AND ANXIETY DISORDERS

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

[1]START Clinic for Mood and Anxiety Disorders

Background: The comorbidity between Attention-Deficit Hyperactivity Disorder (ADHD) and psychiatric disorders including generalized anxiety disorder (GAD) has been well documented. Still, many clinicians fail to screen adult patients for ADHD, despite evidence that adolescents with a history of ADHD are significantly more likely to develop anxiety and depression by adulthood. Comorbid ADHD and GAD has been associated with reduced quality of life and increased risk of self-harm. The aim of this study was to determine the percentage of patients with under- or misdiagnosed ADHD referred for the treatment of mood and anxiety disorders; and examine predictive factors associated with treatment-resistance and suicidality in patients with GAD.

Methods: Data was collected from consecutive referrals (N = 160) to a tertiary-care mood and anxiety clinic. Diagnosis was established by the Mini International Neuropsychiatric Interview Plus (MINI) 6.0.0, ADHD module, and semi-structured interview. Chi-square and logistic regression analyses were performed to assess group differences and predictive factors.

Results: Adult ADHD was present in 36.9% of referrals, 29.4% had comorbid anxiety, and 20.6% had comorbid depression. Misdiagnosed ADHD occurred in 28.7% of referrals □2(4) = 44.8, $p < .001$, $\Phi = .529$. In treatment-resistant referrals 38.2% of GAD and 34% of depression had comorbid ADHD, with 4.4% and 100% undetected respectively. The main predictive factor of misdiagnosis was number of referral diagnosis □2(9) = 39.5, $p < .001$, $\Phi = .597$. Factors predictive of undiagnosed adult ADHD included sex (65.4% males, $p < .031$), alcohol ($p = .010$) and substance dependence/abuse ($p = .047$), and number of diagnoses ($p < .001$). Chronic anhedonia ($p = .042$) and alcohol dependence/abuse ($p = .025$) predicted suicidal ideation, whereas substance abuse was associated with suicide attempt ($p = .013$).

Conclusions: ADHD is a common and treatable disorder that it is often under- or misdiagnosed in adults presenting with mood and anxiety disorders. Among those with treatment-resistant GAD, unrecognized ADHD may explain risky behaviors, multiple referral diagnoses and failed medications; whereas chronic anhedonia may be a prognostic indicator of unrecognized ADHD and suicidality. This study signifies the importance of early and accurate diagnosis of ADHD in adults presenting with mood and anxiety disorders. Increased awareness and use of screening tools may allow for selection of targeted treatment and improved clinical outcomes.

23. ATTENTION DEFICIT HYPERACTIVITY DISORDER: A PREDICTIVE FACTOR OF TREATMENT-RESISTANCE IN ADULTS DIAGNOSED WITH GENERALIZATION ANXIETY DISORDER

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

[1]START Clinic for Mood and Anxiety Disorders

Background: The comorbidity between attention deficit hyperactivity disorder (ADHD) and anxiety is common. Among the most commonly prescribed treatment for generalized anxiety disorder (GAD) are antidepressants. Research has demonstrated that comorbid ADHD is associated with poor outcomes and treatment resistance in depressed patients prescribed selective serotonin reuptake inhibitors (SSRIs). Yet, little is known about the influence of comorbid ADHD on treatment response to antidepressants in patients with GAD. The aim of this study was to assess the prevalence of ADHD in patients referred for the treatment of mood

and anxiety disorders and identify predictive factors of treatment resistance in those that met criteria of comorbid GAD and ADHD.
Methods: Data was collected from consecutive new referrals (N = 97) to a tertiary-care mood and anxiety clinic. Diagnosis was established by the Mini International Neuropsychiatric Interview Plus (MINI) 6.0.0, ADHD module, and semi-structured psychiatric assessment. Treatment-resistance was defined as failure of two or more antidepressants/anxiolytics for adequate treatment dose and duration. Chi-square analyses were performed to assess group differences and predictive factors. Logistic regression was conducted on significant predictors to assess direct effect and obtain odd ratios (ORs).
Results: The result indicated that undetected ADHD was present in 34% of mood and anxiety referrals, 39.2% of patients with GAD, and 45.6% of those with GAD who failed two or more medications. The presence of undetected ADHD ($p = .023$, OR = 5.17), social phobia ($p = .015$, OR = 382), and number of referral diagnoses ($p < .001$, OR = 2.99) were significantly predictive of treatment resistant GAD. Whereas, the number of psychiatric diagnoses ($p < .001$, OR = 3.77), past SSRI failure ($p < .039$, OR = 2.64), and number of SSRI failures ($p < .38$), OR = 3.77) were predictive of undetected ADHD. A significantly higher percentage of patients with undetected ADHD also met criteria for social phobia ($p < .001$, OR = 6.69) and OCD ($p = .031$, OR = 3.33) in those with treatment resistance.
Conclusions: These results support previous findings that ADHD and GAD are highly comorbid disorders. This study demonstrated that ADHD is often unrecognized in adult referred for the treatment of GAD and multiple diagnoses and past SSRI failure are indicative of patients being diagnosed with treatment-resistance. This signifies the importance of accurate screening for adult ADHD in GAD patients presenting with treatment resistance.

24. LONGITUDINAL RELATION BETWEEN INFANT MOTOR ACTIVITY AND CHILDHOOD ADHD SYMPTOMS: MODERATION BY MATERNAL SENSITIVITY

Natalie Miller*[1], Andrea Chronis-Tuscano[1], Kathryn Degnan[2], Nathan Fox[1]

[1]University of Maryland - College Park, [2]Catholic University of America

Background: Higher levels of infant motor activity may be an early temperament precursor to ADHD symptoms, however little is known about how the early caregiving environment (e.g., parenting behaviors) shape the course of ADHD. Following from a stress-diathesis model, it is possible that parenting behaviors might exacerbate or attenuate this temperament risk for ADHD symptoms. However, our understanding of these processes is limited as no prospective longitudinal study has examined parenting behaviors within the context of moderating temperament risk for ADHD. Thus, using longitudinal data from infancy to childhood, the current study examined the moderating role of sensitive parenting on the relation between infant motor activity and childhood ADHD symptoms. We predicted the relation between motor activity and ADHD symptoms would be strongest at lower levels of sensitive parenting.
Methods: We tested these links using a sample of 291 mother-child dyads (45% male). Motor activity was assessed at 4 months through observation. Sensitive parenting behaviors were assessed at 9 months by observation during mother- and child-led structured tasks. Finally, ADHD symptoms were assessed by a composite of parent- and teacher-report using the SNAP-IV at 7 and 9 years respectively. Hierarchical regression models were generated to predict inattentive and hyperactive symptoms separately. For both models motor activity, sensitive parenting, and child gender were entered in step one, and the interaction term between motor activity and sensitive parenting was entered in step two.
Results: As predicted, 4 month motor activity was predictive of 9 year inattentive symptoms, but only at lower levels of 9 month sensitive parenting. Contrary to prediction, motor activity

was not significantly related to hyperactive symptoms, and this relation was not moderated by sensitive parenting.
Conclusions: Infant motor activity was predictive of child inattentive symptoms. Among children with higher motor activity, sensitive parenting may mitigate risk for inattentive symptoms. Although the links between motor activity and ADHD symptoms have been previously reported, this is the first study to examine how early parenting behaviors might moderate these relations.

25. EMOTION DYSREGULATION INCREASES IN CIGARETTE SMOKERS WITH ADHD AFTER SMOKING ABSTINENCE

John Mitchell*[1], Carl Lejuez[2], F. Joseph McClernon[1], Jean Beckham[3], Scott Kollins[1]

[1]Duke University Medical Center, [2]University of Kansas, [3]Durham, NC Veterans Affairs Medical Center

Background: Cigarette smoking is robustly associated with attention-deficit/hyperactivity disorder (ADHD). Although elevated in ADHD samples, little is known about emotional dysregulation as a behavioral mechanism that may account for this comorbid relationship. This study examined the role of emotion dysregulation as a maintenance factor for cigarette smoking in adults. Emotion dysregulation was predicted to be higher in ADHD smokers (a) at baseline and (b) after 24-hour smoking abstinence in comparison to non-ADHD smokers.
Methods: Cigarette smokers with (n = 19) and without (n = 20) ADHD completed a baseline session and two experimental sessions: smoking as usual (i.e., smoking satiated) and after biochemically-verified 24-hour smoking abstinence (i.e., smoking abstinent). Baseline measures included the self-report Difficulties in Emotion Regulation Scale (DERS), and the self-report and clinician ratings of Emotion Regulation subscale from the Deficits in Executive Functioning Scale (ER-DEFS). Experimental sessions also included the DERS and ER-DEFS, as well as the modified Paced Serial Addition Task (mPASAT) and the modified Mirror Tracing Performance Task (mMTPT).
Results: Baseline group differences characterized by greater emotion dysregulation in the ADHD group emerged on the DERS and the ER-DEFS (all p's < .001). For experimental sessions, group (ADHD, non-ADHD) x condition (smoking satiated, smoking abstinence) interactions were not significant. However, main effects for group emerged indicating higher emotion dysregulation in the ADHD group across all measures (all p's < .001). Main effects also emerged for experimental condition (i.e., smoking satiated, smoking abstinent), indicating worsening emotion dysregulation following smoking abstinence (p's < .05 on the ER-DEFS and DERS, p = .09 on the mPASAT).
Conclusions: These findings were characterized by greater emotion dysregulation in adult smokers with ADHD and during smoking abstinence across groups, suggesting that a malleable behavioral mechanism plays a role in smoking both for those with and without ADHD—such findings can inform treatment development.

26. OPEN BOARD

27. DESCRIPTIVE STUDY OF FRIENDSHIPS AND SOCIAL NETWORKS OF ADOLESCENTS WITH ADHD

Barbara Wise*[1]

[1]Indiana Wesleyan University

Background: Although much research has described the social difficulties of children and adolescents with ADHD, no social network analysis has been located that examined the friendship networks of adolescents with ADHD. For clinicians working with adolescents with ADHD, an understanding of their friendships and social networks will assist in understanding their types of social difficulties, providing accurate anticipatory guidance, and serve as a foundation for building effective interventions for youth with ADHD that are struggling socially.

Research questions

1. How do adolescents with ADHD compare with adolescents without ADHD on measures of social acceptance, friendships, social networks, and extracurricular participation?
2. Are there differences among the ADHD subtypes?

Methods: Descriptive study utilizing school social network data from the National Longitudinal Study of Adolescent to Adult Health, a nationally representative sample with Wave I data collected in 7th through 12th grades. Friendship nominations were collected from students in 122 schools. Adolescents with ADHD symptoms in childhood were identified by retrospective self-report in Wave III (N=703; total analytic sample =9626).

Results: Social acceptance. Youth with ADHD self-reported significantly less social acceptance than those without ADHD across all subtypes.

Friendships. There was no significant difference in those who had one reciprocal friendship among those with ADHD and those without. Those with ADHD were no more likely to be isolates or pendants (to have no or only one social tie) than others. Those with ADHD had similar strengths of ties with their friends as others.

Social network measures. There was no difference in popularity (in-degree) or proximity prestige (a measure of the popularity of those who nominate one) among those with ADHD than others, although those with inattentive ADHD reported fewer friends (out-degree) on average than others. Those with inattentive ADHD also had lower centrality and reach within their social networks.

Extracurricular activities. Youth with ADHD had no significant difference in the total number of extracurricular activities with which they were involved than others, but were significantly less likely to be involved in an academically focused extracurricular.

Conclusions: This study found few social deficits in adolescents with ADHD, which contrasts significantly with much of the literature. As a large population based study, those with a broader range of ADHD severity are identified, compared to clinical studies. Further study to subset those with significant difficulties and look for correlates could be very useful.

Perceived lack of social acceptance was striking among those with ADHD, given the minimal differences in actual friendships and social network measures. This may reflect that while those with ADHD had friends, those friends may not have been in prestigious cliques; social acceptance can mean prestige to an adolescent rather than number of people that name the youth as a friend. A more detailed analysis of who adolescents with ADHD are friends with, rather than simply that they have friends, would be valuable. In clinical practice, the results of this study may allow clinicians to offer reassurance to younger children and parents of children with ADHD that by adolescence the majority of those with childhood ADHD appear to function well socially.

28. FURTHER EVIDENCE OF HIGH LEVEL OF PERSISTENCE OF PEDIATRIC BIPOLAR-I DISORDER FROM CHILDHOOD ONTO LATE ADOLESCENT YEARS: A ONE YEAR REPLICATION LONGITUDINAL FOLLOW-UP STUDY

Janet Wozniak*[1], Rebecca Wolenski[1], Maura Fitzgerald[1], Stephen Faraone[2], Gagan Joshi[3], Mai Uchida[3], Joseph Biederman[3]

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

Background: Pediatric Bipolar (BP)–I disorder affects a sizeable minority of children and is associated with high levels of morbidity and disability. Despite longitudinal course being a key validation criteria for any psychiatric disorder, relatively few studies have assessed the persistence of pediatric BP-I disorder over time. The main aim of this study was to replicate findings from our four-year follow up study examining rates of persistence of pediatric bipolar-I disorder onto adolescent years. Additionally, we intended to investigate different definitions of remission at follow-up, including persistence of full threshold BP-I disorder as well as the presence of subsyndromal mania and depression.
Methods: We conducted a one-year replication study to our original prospective follow-up study of 78 youth, ages 6-17 years, with BP-I disorder at ascertainment, who were followed up into their adolescent years (14.9 ± 3.8). All subjects were comprehensively assessed with structured diagnostic interviews, neuropsychological testing, psychosocial, educational and treatment history assessments.
Results: Of the 78 BP-I participating youth, 68 were re-accessioned after one year. Of these, 63% continued to meet full (50%) or subthreshold (13%) diagnostic criteria for BP-I and 18% continued to have full or subthreshold Major Depressive Disorder (MDD). Only 19% of BP-I youth were euthymic at the 5-year follow-up.
Conclusions: This one-year replication follow-up study further documents the high level of persistence of pediatric BP-I from childhood onto mid and late adolescent years. The results provide compelling evidence of the morbidity and dysfunction associated with this disorder and its many forms. This study adds to a small literature on the persistence of pediatric bipolar disorder and the critical need for early identification and intervention.

29. OPEN BOARD

**30. DOES EXPOSURE TO PARENTAL SUBSTANCE USE DISORDERS INCREASE OFFSPRING RISK FOR A SUBSTANCE USE DISORDER? A LONGITUDINAL FOLLOW-UP STUDY INTO YOUNG ADULTHOOD

Amy Yule*[1], Timothy Wilens[1], MaryKate Martelon[2], Joseph Biederman[1]

[1]Harvard Medical School & Massachusetts General Hospital, [2]Massachussetts General Hospital

Background: The main aim of this study was to re-examine the risk of exposure to parental substance use disorders (SUD, alcohol or drug abuse or dependence) on the risk for SUD in offspring with and without attention deficit hyperactivity disorder (ADHD) followed onto young adult years during the peak age of risk to develop a SUD.
Methods: Subjects were derived from two longitudinal case-control studies of probands 6 to 17 years with and without DSM-III-R ADHD of both sexes and their parents followed for ten years onto young adulthood. Probands with a parental history of non-nicotine SUD were

included in this analysis. Exposure to SUD was determined by active non-nicotine parental SUD while the parent was living with their child after birth. Cox proportional hazard models were used to calculate the risk of non-nicotine SUD in offspring.
Results: 171 of the 404 probands reassessed at ten-year follow up had a family history of parental SUD. 102 probands were exposed to active parental SUD. The average age of our sample was 22.2 ± 3.5 years old. Exposure to maternal, but not paternal, SUD increased offspring risk for an alcohol use disorder in young adulthood independently of ADHD status (OR: 2.7 ; 95% CI: 1.1, 6.9; p=0.04).
Conclusions: Exposure to maternal SUD increases the risk for an alcohol use disorder in offspring ten years later in young adult years irrespective of ADHD status.

31. FURTHER EVIDENCE OF THE DIAGNOSTIC UTILITY OF THE CHILD BEHAVIOR CHECKLIST FOR IDENTIFYING PEDIATRIC BIPOLAR I DISORDER

Amy Yule*[1], Maura Fitzgerald[2], Timothy Wilens[1], Janet Wozniak[1], K. Yvonne Woodworth[2], Alexa Pulli[2], Mai Uchida[1], Stephen Faraone[3], Joseph Biederman[1]

[1]Harvard Medical School & Massachusetts General Hospital, [2]Massachusetts General Hospital, [3]SUNY Upstate Medical University & University of Bergen, Norway

Background: Pediatric bipolar (BP) disorder is a prevalent and highly morbid disorder. Early identification of children with this diagnosis in the clinical setting can allow therapeutic approaches to help mitigate the poor outcomes associated with pediatric BP disorder. The main aim of this study was to assess the diagnostic utility of a unique profile derived from the Child Behavior Checklist (CBCL), the CBCL-BP profile, to identify children with BP-I in the clinical setting.
Methods: This study examined the ability of the CBCL-BP profile to identify children with and without a structured interview diagnosis of BP-I disorder using receiver operating characteristic (ROC) curves. Subjects were derived from four independent datasets of children with and without attention deficit hyperactivity disorder (ADHD) and BP-I disorder evaluated at baseline. All subjects had structured clinical interviews with raters who were blinded to subject ascertainment status.
Results: The overall sample of 661 subjects had an average age of 11.7 ± 3.3 years, was 57% male, and 94% Caucasian. 130 (19.7%) of subjects had a structured interview derived diagnosis of BP-I disorder. The ROC analysis of the CBCL-BP profile in children with and without BP-I disorder yielded an area under the curve of 0.91. A score of ≥195 on the CBCL-BP profile correctly classified 86% of subjects with BP-I disorder with 80% sensitivity and 87% specificity.
Conclusions: The CBCL-BP profile is an efficient tool to identify children with a structured interview derived clinical diagnosis of BP-I disorder.

32. SCREENING FOR ADHD AND IMPAIRMENT IN A GENERAL OUTPATIENT PSYCHIATRIC SAMPLE OF ADULTS

Dara Babinski*[1], James Waxmonsky[1], Edward Bixler[1], Duanping Liao[1], Amanda Pearl[1], Dahlia Mukherjee[1], Daniel Waschbusch[1], Erika Saunders[1]

[1]Pennsylvania State University, College of Medicine

Background: Approximately 4% of adults in the United States are diagnosed with ADHD, although there has been little formal examination of its prevalence and associated morbidity in

clinical samples. The goal of this study was to examine the prevalence of ADHD in an adult outpatient setting and to examine the unique association between ADHD symptoms and functional impairment controlling for co-occurring mental health concerns.
Methods: A total of 492 adults (69.7% female; Mage=40.84, SD=14.83) completed ratings of ADHD, impairment, and co-occurring psychopathology upon initiating mental health services. The Adult ADHD Self-Report Scale (ASRS) assessed DSM-IV ADHD symptoms, the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) assessed overall impairment, and the DSM-5 Self-rated Level 1 Cross-Cutting Symptom Measure was used to assess co-occurring psychopathology. Given the substantial co-occurrence of ADHD and depression, suicidality, mania, anxiety, sleep problems, and substance abuse, these items were separately selected from the Level 1 Cross-Cutting as covariates.
The prevalence of ADHD was assessed using DSM-IV and DSM-5 symptom count criteria. Associations between ADHD symptoms and impairment were calculated using the average impairment score across WHODAS 2.0 domains. Follow-up step-wise linear regression including age, gender, depression, anxiety, sleep difficulty, suicidality, substance abuse, and ADHD symptoms were conducted to examine the unique association between ADHD and impairment.

Results: Using DSM-IV symptom count criteria requiring six or more symptoms of inattention and/or hyperactivity/impulsivity, 40.85% of the sample was identified as meeting symptomatic criteria for ADHD (110 inattentive type, 24 hyperactive/impulsive type, and 67 combined type). A total of 51.83% met DSM-5 symptom count criteria (125 inattentive presentation, 30 hyperactive/impulsive presentation, and 100 combined presentation).
ADHD symptoms were associated with mean impairment on the WHODAS 2.0 ($r=.52$, $p<.001$), and continued to explain unique variance in overall impairment when controlling for age, gender, and co-occurring mental health concerns, $F(9, 491)=39.17$, $p<.001$, R2.=.42. Age, depression, anxiety, substance abuse, mania, and sleep difficulty also explained a significant portion of variance in impairment, while gender and suicidality did not.

Conclusions: The prevalence of ADHD identified in this outpatient sample was nearly 10 times higher than rates identified in epidemiological studies, and ADHD symptoms meaningfully contributed to the functional impairment in patients with a wide range of psychiatric symptoms. These results emphasize the importance of further assessment of ADHD including diagnostic interview and collateral rating in standard mental health care for adults.

33. ITEM RESPONSE THEORY ANALYSIS OF THE BEFORE SCHOOL FUNCTIONING QUESTIONNAIRE AND PARENT RATING OF EVENING AND MORNING BEHAVIOR SCALE, REVISED IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Stephen Faraone*[1], Norberto DeSousa[2], F. Randy Sallee[2], Bev Incledon[2], Timothy Wilens[3]

[1]SUNY Upstate Medical University, [2]Ironshore Pharmaceuticals & Development, Inc., [3]Harvard Medical School & Massachusetts General Hospital

Background: The Before School Functioning Questionnaire (BSFQ) and Parent Rating of Evening and Morning Behavior Scale, Revised (PREMB-R) are two validated rating scales that measure temporal at-home functional impairment in children with attention-deficit/hyperactivity disorder (ADHD). Using item response theory (IRT) methods, the objectives of this study were to: (1) evaluate the performance of individual BSFQ and PREMB-

R items in relation to their respective underlying latent traits (i.e., early morning [EMF] impairment for the BSFQ and PREMB-R morning subscale [AM], and late afternoon/evening functional impairment for PREMB-R evening subscale [PM]); and (2) determine whether the BSFQ and PREMB-R AM are measuring the same underlying construct of EMF impairment.
Methods: Data from two randomized, placebo-controlled phase 3 trials of DR/ER-MPH (formerly HLD200), a delayed-release and extended-release methylphenidate, in children (6-12 years) with ADHD were analyzed. Baseline and treatment response data on the BSFQ, PREMB-R AM, and PREMB-R PM scales were evaluated using a non-parametric IRT approach with kernel smoothing. Option characteristic curves were constructed to demonstrate the probability of endorsing a particular response on each item across the different levels of the underlying latent trait. Item information curves were used to illustrate how much information each item contributes as a function of the overall latent trait. Discrimination (ability of an item to discriminate between individuals at high and low levels on the underlying latent trait) and response location (equivalent to response difficulty or probability of endorsing a particular level of severity on the underlying latent trait) parameters were estimated for all items. In separate analyses, the latent trait was also defined for the total BSFQ and PREMB-R AM score to determine if these instruments are measuring the same construct.
Results: All items on the BSFQ, PREMB-R AM, and PREMB-R PM were good at discriminating their respective latent traits. Discrimination estimates ranged from 1.9 to 4.6 for BSFQ, 2.5 to 4.4 for PREMB-R AM, and 1.3 to 3.4 for PREMB-R PM. The most discriminating items were "attention" on the BSFQ, "getting ready in the morning" on the PREMB-R AM, and "inattentive during the late afternoon/evening" on the PREMB-R PM. Response locations were well dispersed across the full range of the latent trait on the BSFQ (-0.9 to 1.8), PREMB-R AM (-0.5 to 1.1), and PREMB-R PM (-1.1 to 1.6). The most difficult items to endorse were "getting to school" on the BSFQ, "getting up and out of bed" on the PREMB-R AM, and "falling asleep" on the PREMB-R PM. In the combined analysis of BSFQ and PREMB-R AM, discrimination estimates ranged from 1.9 to 4.1 and the response locations of all items on both scales overlapped across the latent trait continuum (-0.8 to 1.1), indicating that both instruments measure the same construct of EMF impairment. Additionally, there were no reversed response locations with increasing levels of the latent trait.
Conclusions: All items forming the BSFQ, PREMB-R AM, and PREMB-R PM performed very well in relation to their underlying latent traits, and both BSFQ and PREMB-R AM were found to measure the same underlying construct of EMF impairment.

34. SOCIAL ANXIETY AND SELF-EFFICACY IN YOUNG ADULTS WITH ADHD SYMPTOMS: ASSESSING THE USE OF THE ADULT ADHD SELF-REPORT SCALE (ASRS-V1.1) PART A

Tom Buchanan[1], Meghan Leahy*[2], Roberta Waite[3]

[1]Mount Royal University, [2]Leahy Learning, [3]Drexel University

Background: Research has effectively demonstrated that ADHD is a chronic and lifelong disorder which creates challenges. These challenges are salient for young adults attending college who experience a dramatic transition to post-secondary institutions. Many students with ADHD remain undiagnosed and do not receive the necessary support to achieve success. In this project, we have two objectives: 1) highlight the importance of the ADHD Adult Self-Report Scale (ASRS-v1.1, Part A) for identifying ADHD symptoms using survey methodology in comparison to self-report diagnosis of ADHD, and; 2) analyze how this indicator is a reliable predictor for self-efficacy and anxiety.

Methods: The data came from a convenience sample of general education classes of a university in the Southeast United States. While this sample is not a random probability sample, it is representative of the student population generated by sampling students from general education classes during various times and days including one night class. The final sample consists of 553 college university students 18 to 25 years old. Participants completed Part A of the Adult ADHD Self-Report Scale (ASRS-v1.1) to indicate how frequently they experience certain behaviors. Global Self-efficacy was assessed using 6 items from the 17-item global self-efficacy scale constructed and tested by Sherer et al. (1982). This scale assesses individuals' perceptions of their own ability to attempt and accomplish difficult tasks. Social Anxiety was assessed using two subscales of 6 items each from the Liebowitz Social Anxiety Index (1987); it examines the participants' perceptions of the level of fear or anxiety they have felt in different situations. The second subscale assesses the frequency of attempting to avoid the scenarios from the first scale. ANOVA and OLS regression analyses were performed in pursuit of the aforementioned objectives.
Results: Participants scoring 4 or higher on Part A of the ASRSv1.1 indicate symptomology associated with Adult ADHD. ANOVA results demonstrate participants in the 4 or more group are very similar to the other two groups on the demographic measures, generally. This group reports lower self-efficacy and higher rates of anxiety-related behavior (both types). Finally, participants in the 4 or more group have a higher, albeit small, rate of self-reporting ADHD. The OLS regression results demonstrate higher levels of ADHD symptoms on the ASRS are associated with lower self-efficacy and higher levels of anxiety (fear and avoidance). However, self-report diagnoses of ADHD are not significantly associated with the outcomes.
Conclusions: ASRS (Part A) appears to be a better measure of ADHD than self-report diagnoses for projects utilizing survey methodology for larger samples. Also, symptoms related to ADHD are associated with lower self-efficacy and higher levels of social anxiety among university students. This study has implications for university administrators and service providers who provide support to students experiencing ADHD.

35. SLUGGISH COGNITIVE TEMPO IN ADULT OUTPATIENTS SEEKING AN ADHD EVALUATION: A PSYCHOMETRIC ANALYSIS OF THE BAARS-IV SCT SUBSCALE

Jessica Lunsford-Avery*[1], Scott Kollins[1], Julia Schechter[1], Maggie Sweitzer[1], Cara Lusby[1], Jessica Solis Sloan[1], John Mitchell[1]

[1]Duke University Medical Center

Background: Accumulating evidence suggests that Sluggish Cognitive Tempo (SCT; a set of symptoms including mental fogginess, slowed cognition/behavior, and daydreaming) is an important clinical construct that is distinct from ADHD yet associated with significant functional impairment. Measures of SCT have proven reliable and valid in child samples, and more recently, SCT surveys have been validated in college students. However, to date, no studies have examined the psychometric properties of a SCT measure in an adult clinical population, an important gap as assessment of SCT may represent a useful tool to clarify diagnosis and inform treatment in clinical settings. The current study examines the internal reliability, factor structure, and convergent validity of the SCT subscale of the Barkley Adult ADHD Rating Scale-IV (BAARS-IV) in an outpatient sample of adults seeking an ADHD assessment.
Methods: Adult participants (n = 124) were recruited from an outpatient psychiatry clinic at a university medical center. All participants were seeking an evaluation for ADHD (age M = 31.13, SD = 11.47; 50% female, 72% Caucasian). Participants and a collateral reporter (e.g.,

spouse, parent, or friend) each completed the 9-item SCT subscale of the BAARS-IV and the Conners' Adult ADHD Rating Scale - Long Form (CAARS; self- and observer-reports).
Results: Both the self- and other-report versions of the BAARS-IV SCT subscale demonstrated good internal consistency (Cronbach's α = .79 and .82, respectively). Principal components analyses (using a varimax rotation) conducted separately for self- and other-reports consistently identified three factors: Daydreamy (4 items), Sluggish (3 items), and Low Persistence (2 items). Pearson correlations indicated significant relationships between the SCT total score and all CAARS subscales for both self- and other-reports. Interestingly, while the Daydreamy and Low Persistence factors of the SCT were highly associated with CAARS subscales across self- and other-reports, the Sluggish SCT factor was significantly related to the "Problems with Self Concept" CAARS subscale only, and was not significantly correlated with any of the ADHD-related subscales of the CAARS.
Conclusions: Findings from the current study extend prior studies focused on population-based or college student samples to support the SCT subscale of the BAARS-IV as a reliable and valid measure of sluggish cognitive tempo in a clinical sample of adults seeking an ADHD evaluation in an outpatient setting. Notably, we identified three facets of SCT that comprise the overall total score. This factor structure is consistent with prior literature assessing SCT in child clinical samples, but differs from studies with college students, which have suggested a single SCT factor. While the Daydreamy and Low Persistence aspects of SCT were associated with ADHD symptoms, the Sluggish factor was associated only with problems with self-concept, which is consistent with prior findings linking SCT to socioemotional difficulties (i.e., depression, anxiety, and low self-esteem). This study highlights the potential of SCT measures to inform diagnostic presentation and treatment planning in clinical settings. Future studies should examine links between SCT and clinical symptoms, functional impairment, and treatment response in clinical samples of adults with ADHD.

36. LATENT CLASS ANALYSIS OF PREVISIT PARENT RATINGS AS PREDICTORS OF ADHD COMORBIDITIES

Alison Pritchard*[1], Luke Kalb[1], T. Andrew Zabel[1], Lisa Jacobson[1]

[1]Kennedy Krieger Institute

Background: Neuro/psychological assessment of patients with ADHD helps identify comorbidities such as learning and emotional disorders which have implications for treatment. These assessments, however, can be lengthy, expensive, and have long wait lists. The present study tested an analytic approach for providing more targeted triage and evaluation, with the goal of reducing costs and wait times while maintaining effective patient care.
Methods: Participants included 1181 youth aged 4-19 (M=10.1y, SD=3.7y; 61% male) seen for outpatient evaluation in a hospital-affiliated neuropsychology clinic. Latent class analyses (LCA) were used to identify clusters of children based on guardian behavioral ratings provided prior to visit. Fit statistics (AIC/BIC, entropy, VLMR, BLRT) and clinical value were employed to select the optimal model. The validity of latent classes was evaluated using performance-based measures, additional parent ratings, and the clinician diagnoses resulting from the visit. These metrics were available on roughly a third of the sample, as most of the youth were still awaiting their appointment. The LCA employed four parent-reported indicators to determine class membership: Revised Children's Anxiety and Depression Scale, ADHD Rating Scale 5, Colorado Learning Difficulties Questionnaire, and Impairment Rating Scale.
Results: A 4-class model was chosen as the best fit for the data with the greatest clinical value. Classes included: 1. Subthreshold (21% of sample) – few symptoms of any kind, minimal impairment; 2. Academic (36%) – learning difficulties in reading and math and associated

impairment, but few other concerns; 3. Academic+Inattention (26%) – symptoms of inattention, academic concerns and considerable impairment, without emotional concerns; 4. Complex (17%) – symptoms and impairment across most domains. After adjusting for age, sex, race, and parental education, Subthreshold class scores fell within 1 SD of the mean across measures. In relation to the Subthreshold class, the Academic class had lower IQ (M=86) and academic skills (Math=87, Reading=86) but not adaptive functioning (M=83) or emotional/behavioral problems (M=52). The Complex class had elevated emotional/behavioral scores (M=61) and low adaptive functioning (M=76) but comparable IQ and academic performance, relative to the Subthreshold class. While these findings support the validity of the Subthreshold, Academic, and Complex classes, the validity of the Academic+Inattention class was not supported, as this class had elevated emotional/behavioral concerns (M=61), but was similar to the Subthreshold class in terms of IQ, adaptive functioning, and academic skills. More than 2/3 of patients were diagnosed with ADHD, of which 42% fell in the Complex class, 36% in the Academic class, 12% in the Academic+Inattention class, and 10% in the Subthreshold class.
Conclusions: Nearly half (42%) of ADHD patients presenting for neuro/psychological assessment are likely to be complicated by comorbidities and may require comprehensive evaluation. More than 1/3 of patients with ADHD, those within the Academic class, are unlikely to have emotional, behavioral, or adaptive difficulties and may benefit from a more targeted assessment of attentional and academic skills. Patients in the Subthreshold class are unlikely to show major learning, emotional, behavioral, or adaptive deficits and may represent a relatively uncomplicated group of children with ADHD for whom a still briefer assessment might be appropriate.

37. CAREGIVER SURVEY OF THE BURDEN OF DISEASE IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Brigitte Robertson*[1], Alexandra Khachatryan[1], Michael Andreini[2], Steven Blahut[2], Eitan Shimko[2], Robert Stolper[2], Peter S. Jensen[3]

[1]Shire, [2]Quintiles IMS, [3]University of Arkansas for Medical Sciences

Background: Children and adolescents diagnosed with attention-deficit/hyperactivity disorder (ADHD) face significant social, family, educational, and financial burden. This cross-sectional survey evaluated the burden of illness from the perspective of caregivers of children and adolescents with ADHD currently treated with stimulant medication.
Methods: A 20-minute online survey was administered to caregivers of children and adolescents (aged 6–17 years) diagnosed with ADHD and currently receiving stimulant medication. The burden of ADHD was quantified by caregivers using 5-point Likert scales that ranged from 1 (least severe) to 5 (most severe). Respondents were stratified by their child's current treatment regimen: short-acting or long-acting monotherapy, or multiple medications. Means, medians, frequencies, and ranges were calculated for each question in the surveys for each subject. Caregiver data were combined across current medication type and patient age, and subjected to a statistical analysis by Two-Sample T-Test (for continuous metrics) or Chi Square (for categorical measures).
Results: 300 caregivers of children or adolescents with ADHD (mean [SD] age: 13 [3] years) receiving stimulant medications (long-acting, n=120; short-acting, n=90; multiple therapies, n=90) completed the survey. Regardless of current medication, 43% of caregivers reported that their children experienced a high level of impact of ADHD on daily activities (i.e., responses were within the two most severe Likert categories). Caregivers perceived that children and adolescents experienced a greater impact of ADHD on their daily activities during the school

week (47%) than during the weekend (29%). The greatest burden of ADHD reported was during after-school activities/afternoon homework (45%) followed by early morning (42%) and during evening homework/leisure time (41%). During a typical school week, only 6% of caregivers felt that their child's medication did not wear off during the day, while 39% reported that medication was most likely to wear off during the period of afterschool activities/afternoon homework. Proportions of caregivers reporting a high impact of ADHD on their child's relationships with teachers, friends/classmates and parents/primary caregivers were qualitatively greater for the 6–11 years age group (41%, 37% and 34%, respectively) than older age groups (12–14 years: 31%, 31%, 33%; 15–17 years: 33%, 36%, 32%). Overall, caregivers reported ADHD burden was highest in children and adolescents receiving multiple therapies (51%), followed by those receiving short-acting (46%) or long-acting (36%) stimulants alone.
Conclusions: A large proportion of caregivers with children and adolescents diagnosed with ADHD perceived that the burden of illness remained high despite current treatment. However, the burden was perceived to be higher among those receiving multiple medications than those managed with once-daily, long-acting medications. While caregivers identified challenges across the times of day almost equally, most caregivers reported that their child's medication appeared to wear off later in the day. The impact of ADHD on daily activities was qualitatively highest in the immediate afterschool/homework period. These results support the need for medication strategies that provide symptom coverage across the whole day from early morning through the evening in children and adolescents with ADHD.

Study funded by Shire Development LLC.

38. AT-HOME FUNCTIONAL IMPAIRMENT IN YOUTH WITH ADHD: FACTOR STRUCTURE AND NORM-REFERENCED CUT-OFF POINTS FOR THE BEFORE SCHOOL FUNCTIONING QUESTIONNAIRE AND PARENT RATING OF EVENING AND MORNING BEHAVIOR SCALE, REVISED

Stephen V. Faraone[1], Norberto DeSousa[2], Rick Nullmeier[2], Randy Sallee*[2], Beverly Incledon[2], Timothy Wilens[3]

[1]SUNY Upstate Medical University, [2]Ironshore Pharmaceuticals & Development, Inc., [3]Harvard Medical School/Massachusetts General Hospital

Background: Two validated rating scales have been used in clinical trials to measure temporal at-home functional impairment in children with attention-deficit/hyperactivity disorder (ADHD): 1) Before School Functioning Questionnaire (BSFQ), which assesses early morning functional (EMF) impairment, and 2) Parent Rating of Evening and Morning Behavior Scale, Revised (PREMB-R), which evaluates EMF and late afternoon/evening functional impairment. The objectives were to determine the factor structure and define norm-referenced cut-off points for both instruments.
Methods: A survey was conducted with 1200 respondents derived from a representative US sample of primary caregivers of youth (6-17 years; n=50 per age/gender category). Caregivers were enrolled if their child never had ADHD or had a history of ADHD (past or current untreated). Using a severity scale of 0 to 3 (higher score indicating greater severity), caregivers rated their child's at-home functional impairment on the 20-item BSFQ and 11-item PREMB-R. Because the prevalence of ADHD in this sample (10.1%) was approximately twice the population expectation of 5%, a random number generator deleted half of the ADHD participants to create a modified data set with the goal of estimating cut-offs that would be generalizable to the population. Given the significant effect of age on scores, norm-referenced

percentile cut-offs were computed for four age categories. Norm-referenced percentile cut-offs were calculated for screening risk (80th) and for identifying mild (90th), moderate (93rd), and severe (98th) functional impairment.
Results: Of the 700 children (6-12 years) and 500 adolescents (13-17 years) rated by a caregiver, 1079 had no history of ADHD and 121 had a history of ADHD. As expected, BSFQ fit a 1-factor model, which explained 91.7% of the variance, and PREMB-R fit a 2-factor model, with one factor containing 3 morning items (PREMB-R AM subscale) and the other accounting for 8 late afternoon/evening items (PREMB-R PM subscale). Age and psychiatric comorbidities, but not gender, had significant effects on BSFQ, PREMB-R AM, and PREMB-R PM scores. Youth with ADHD had significantly higher scores than those without ADHD, even after adjusting for comorbidities, and increased age was associated with decreased scores, consistent with other studies demonstrating decreased ADHD symptoms with increased age. After norm-referenced cut-offs were calculated, some cut-points were smoothed to create a set of cut-points that were consistent with the finding that all three scores decrease with age. Across ages, the norm-referenced smoothed cut-off points on the modified data set were defined for screening risk (BSFQ: 21-25; PREMB-R AM: 4-5; PREMB-R PM: 9-11), and for mild (BSFQ: 28-33; PREMB-R AM: 6; PREMB-R PM: 13-15), moderate (BSFQ: 31-36; PREMB-R AM: 6; PREMB-R PM: 15-16), and severe (BSFQ: 42-43; PREMB-R AM: 7-8; PREMB-R PM: 18-19) functional impairment. Cut-offs by age categories will also be presented.
Conclusions: Age-stratified percentile cut-off points derived from norm-referenced data were defined to guide clinicians in determining the severity of ADHD-related at-home functional impairment among youth. These cut-offs are relevant for treatment-naïve as well as treated ADHD patients given that the latter also show substantial functional impairment in the morning hours.

39. ADHD SYMPTOMS AND PERFORMANCE ON THE CHILDREN'S GAMBLING TASK

Sierra Tolbert*[1], Caroline Barry[1], Victoria Saba[1], Alesha Majors[1], Bernard Fuemmeler[2], Scott Kollins[1], Julia Schechter[1]

[1]Duke University Medical Center, [2]Virginia Commonwealth University

Background: ADHD has been linked to affective decision-making and impulsivity in children. The Children's Gambling Task (CGT), a simplified version of the Iowa Gambling Task, is a measure of affective decision-making about events that have emotional or motivationally relevant consequences (i.e., "hot" executive functioning). Improved understanding of associations between ADHD and decision-making may inform teaching strategies in the classroom to better address the needs of children with ADHD symptoms.
Methods: The sample (N=165) was drawn from an ongoing longitudinal study comprised of mother-child dyads recruited from the community in Durham, NC. Mothers and teachers (N=111) completed behavioral questionnaires when children were 4-11 years old (mean=6.73 years, SD=1.88 years, 46.1% male). Parents and teacher ratings on the Behavior Assessment for Children, 2nd Edition (BASC-2) were used to evaluate ADHD-relevant constructs (Hyperactivity and Attention Problems subscales). Children completed the CGT individually with a trained administrator and had the opportunity to earn M&M's based on their performance. Successful learning on the CGT was indicated by selection of more advantageous than disadvantageous cards across five blocks (10 trials/block). Linear regression was used to assess the relationship between parent and teacher reported ADHD symptoms and CGT performance on the final block.

Results: Controlling for child age and gender, teacher rated attention problems on the BASC predicted to significantly poorer performance on the final trial of the CGT, β=-.22, t(109)=-2.24, p=.028. However, parent ratings of attention problems on the BASC, β=-.04, t(159)=-.47, p=.64, were not associated with CGT performance. In addition, CGT performance was not predicted by parent, β=-.08, t(159)=-1.05, p=.29, or teacher, β=-.13, t(109)=-1.32, p=.19, ratings of hyperactivity.
Conclusions: In a community sample, greater teacher-rated attention problems were associated with poorer ability to make advantageous choices on a decision-making task for children; however, parent-rated attention problems and hyperactivity scores were not associated with task performance. Findings suggest that teacher observations of attention may be a better indicator of decision-making and learning during childhood and underscore importance of multiple informants from different settings when assessing ADHD symptoms. These findings have implications for reward learning and decision-making in the classroom. Further investigation with larger sample size will be important to better understand children's ADHD symptoms in relation to learning trends and can inform teaching strategies.

**40. RESPONSE TIME ADJUSTMENT IN THE STOP SIGNAL TASK SERVE AS A MARKER OF REINFORCEMENT LEARNING: DEVELOPMENT IN TYPICALLY DEVELOPING AND ADHD CHILDREN AND ADOLESCENTS:

Russell Schachar*[1], Annie Dupuis[2], Jennifer Crosbie[1], Paul Arnold[3], Mohsen Soltanifar[1]

[1]University of Toronto, [2]The Hospital for Sick Children, [3]University of Calgary

Background: Adjusting speed to maintain fast and accurate performance is critical to goal-directed behavior. Typically, people slow down when they make mistakes. Post-error slowing is a critical function of the dopamine-mediated pathways involved in reinforcement learning. Little is known about healthy development of temporal processes and about the way these adjustments are affected in ADHD-- a condition which is presumed to involve atypical reinforcement learning.
Methods: We examined development of response time adjustments in the stop signal task (SST) in 13,709 typically developing and 450 individuals with self-reported ADHD aged 6-17 years. The SST involves two tasks-a go task in which participants must make a simple choice response as quickly and as accurately as they can and a stop task in which on a subset of trial participants are instructed by a tone to try to stop their response on that particular trial. We measured response time adjustments across four trial types: correct and incorrect go trials, successful (stop-inhibit) and failed (stop-respond) trials.
Results: People sped more after correct than after incorrect go responses and slowed more after failed (stop-respond) stop trials than after successful (stop-inhibit) trials. Greater slowing after stop-respond trials was associated with better response inhibition; greater slowing after stop-inhibit trials was associated with poorer response inhibition. Individuals with self-reported ADHD demonstrate an altered pattern of temporal adjustments.
Conclusions: Response time adjustments were evident in children as young as age 6, developed throughout childhood, plateaued by age 10 and were deviant in ADHD. Results were consistent with the predictions of the error detection and shifting goal priority hypotheses for adjustments. Examination of response time adjustments in the context of the stop signal task provides a feasible marker of reinforcement in health and disease.

41. COPY NUMBER VARIANTS IN BRAIN-RELATED GENES ARE ASSOCIATED WITH NEUROPSYCHIATRIC TRAITS IN CHILDHOOD

Russell Schachar*[1], Christie Burton[1], Mehdi Zarrei[1], W Engchuan[1], Daniel Merico[1], J MacDonald[1], B Xiao[1], Andrew Paterson[1], Lisa Strug[1], Christian Marshall[1], Jennifer Crosbie[1], Paul Arnold[2], Steven Scherer[1]

[1]University of Toronto, [2]University of Calgary

Background: Rare copy number variants (CNVs) likely play an important role in common childhood neuropsychiatric disorders such as ADHD and OCD. These disorders represent the extremes of broadly distributed behavioural traits that are influenced by underlying variation in fundamental cognitive processes such as response inhibition. Using behavioural and cognitive trait-based approaches in population samples can help reduce heterogeneity and improve power to detect rare CNVs associated with these disorders. Currently we do not know the prevalence of CNVs related to neuropsychiatric disorders in youth in the general population. Using the Spit for Science sample (Toronto, Canada), we examined the association of rare CNVs with ADHD, OCD and response inhibition traits.
Methods: Rare copy number variants (CNVs) likely play an important role in common childhood neuropsychiatric disorders such as ADHD and OCD. These disorders represent the extremes of broadly distributed behavioural traits that are influenced by underlying variation in fundamental cognitive processes such as response inhibition. Using behavioural and cognitive trait-based approaches in population samples can help reduce heterogeneity and improve power to detect rare CNVs associated with these disorders. Currently we do not know the prevalence of CNVs related to neuropsychiatric disorders in youth in the general population. Using the Spit for Science sample (Toronto, Canada), we examined the association of rare CNVs with ADHD, OCD and response inhibition traits.
Results: After stringent quality control, 4815 (85.4%) of participants remained with a total of 9,490 rare CNVs (1.97/individual on average). We observed CNVs affecting 23 genomic loci previously implicated in neurodevelopmental conditions (e.g. 22q11.2) in 59 (1.2%) of participants. Other large CNVs affecting known psychiatric genes (e.g., ASTN2, NRXN1) were also identified. Significantly more deletions (>500kb; $p = 0.04$) and enrichment of deletions in genes involved in synapse structure, neuron projection and neurophenotypes in mice ($p < 0.03$) were observed for ADHD traits. For response inhibition, there were significantly more duplications (50-500kb; $p = 0.004$), a trend towards more deletions ($p = 0.07$), more deletions of genes related to brain structure and function ($p < 0.008$) and duplications in genes highly and specifically expressed in the brain for response inhibition ($p = 0.006$). There was no association between overall burden and OCD traits but duplications in genes related to synaptic function and neurotransmission were enriched for this trait ($p < 0.01$).
Conclusions: In a large pediatric general population sample, brain-related CNVs were associated with neuropsychiatric traits in children although the pattern of enrichment differed between ADHD, OCD and response inhibition. Our results replicate several previous CNV burden findings for ADHD and OCD suggesting a similar genetic architecture between traits and disorders. Our approach shows the feasibility of CNV analysis and quality of CNV data from the HumanCoreExome array in a large population based sample.

42. HERITABILITY OF NEUROPSYCHOLOGICAL SUBTYPES IN ADHD

Anne Arnett*[1], Bruce Pennington[2], Erik Willcutt[3]

[1]University of Washington, [2]University of Denver, [3]University of Colorado

Background: Attention deficit hyperactivity disorder (ADHD) is associated with a heterogeneous phenotype and etiology. Neuropsychological deficits are frequently proposed as

endophenotypes of ADHD; however, no single deficit has been sufficient or necessary to explain variance in ADHD severity. A recent study identified six neuropsychological profiles associated with ADHD (Fair et al., 2012), suggesting homogenous cognitive subtypes that may explain phenotypic variance in the disorder. Given that heritability in ADHD symptom severity is high (~.70), estimation of the heritability of cognitive profiles could offer insight into unique etiological mechanisms associated with homogenous subtypes of ADHD.
Methods: 1,319 twin pairs (34% monozygotic) and 227 siblings (total N=2,866; age range = 7-19 years) were recruited through the Colorado Learning Disabilities Research Center. The sample included youth affected by ADHD (13%), reading disability (18%) or both (11%), as well as neurotypical controls (58%). Over the course of two full-day visits, participants completed a comprehensive neuropsychological battery including tests of verbal and spatial working memory, processing speed, inhibition and arousal. A research diagnosis of ADHD was assigned to youth if caregiver and teacher ratings on a DSM-IV-TR ADHD checklist indicated at least six symptoms of inattention or hyperactivity/impulsivity.
Results: Latent class analysis of the full sample identified four distinct neuropsychological profiles characterized by 1) slow processing speed, low arousal and poor inhibition, 2) extremely low arousal, 3) average performance across domains, and 4) above average verbal working memory, processing speed and arousal. Logistic regression indicated participants with ADHD or comorbid ADHD + RD were significantly more likely to show one of the first three profiles and less likely to show the fourth profile relative to neurotypical controls (p's<.001). Structural equation ACE modeling indicated heritability of neuropsychological profiles among twins and siblings was h2=.52, with the contribution of non-shared environment at .48 and no significant contribution of shared environment. The model showed excellent fit (χ2[5]=7.577, p=.181; CFI=.99, RMSEA=.03). Constraining the AE parameters to be equal across ADHD and neurotypical controls did not significantly change the model fit (p=.689), indicating heritability of neuropsychological profiles was equal across ADHD and neurotypical groups.
Conclusions: Neuropsychological profiles, rather than universal deficits, may reliably distinguish individuals with ADHD from neurotypical controls and may reflect homogenous etiological subtypes of ADHD. Heritability of these subtypes is lower than that of ADHD overall, suggesting genetic risk for ADHD interacts with environmental factors to impact cognitive performance. Classification of neuropsychological subtypes of ADHD may facilitate precisely tailored behavioral and pharmaceutical interventions. Additional analyses will include estimating heritability of continuous cognitive factors across neuropsychological profiles and describing the comorbid psychiatric phenotype associated with distinct neuropsychological profiles.

**43. REVERSE MICRODIALYSIS STUDIES OF D-, L-, & D,L-AMPHETAMINE-EVOKED DOPAMINE AND NOREPINEPHRINE RELEASE IN THE RAT NUCLEUS ACCUMBENS AND PREFRONTAL CORTEX

Paul Glaser*[1], Peter Huettl[2], Francois Pomerleau[2], Luke Bradley[2], Meagan Littrell[2], Greg Gerhardt[2]

[1]Washington University in St. Louis, [2]University of Kentucky

Background: There are only a few research studies and case reports showing differences in efficacy and side effects of dextroamphetamine and racemic amphetamine products in children and adults with ADHD. Mixed amphetamine salts (Adderall), which contains 25% l-amphetamine, has been used since the early 1990s and more recently 50/50 d,l-amphetamine (Evekeo) has FDA approval for ADHD. There is not yet a good understanding of how l-amphetamine works differentially from d-amphetamine. Our hypothesis is that the differential

clinical effects can be explained by the effects of l-amphetamine on d-amphetamine on evoked dopamine (DA) and norepinephrine (NE) release in critical brain regions implicated in ADHD.
Methods: Reverse microdialysis was performed in the nucleus accumbens and prefrontal cortex of 30 anesthetized male Fischer 344 rats (3-6 months old to measure amphetamine-evoked release of DA and NE. After perfusing the brain with aCSF for 60 mins, clinically relevant doses (1 μM) of 100% d-amphetamine, 50/50 d,l-amphetamine and 100% l-amphetamine was applied to perfusing brain areas at 0.75ul/min for 120 minutes, followed by aCSF for 60 mins. Samples were analyzed using HPLC with electrochemical detection. Blinding was used to minimize bias. Data were analyzed by analysis of variance (ANOVA) statistics with Sidak's and Tukey's corrections for multiple comparisons.
Results: Dopamine (DA) overflow in the prefrontal cortex shows a significant increase for DA between l and dl isomers 140 minutes after introduction of amphetamine ($p = 0.0308$). There was no significant difference between l, dl and d amphetamine isomers, at any time points for NE overflow in prefrontal cortex. NE and DA overflow in the Nucleus Accumbens shows significant increases for DA over NE for each isomer. DA overflow, using combined area under the curves (AUC (0-inf)) measures, is significantly greater for the d (100) vs. l (100) isomers and d (100) vs. dl (50/50) in NAc ($p<0.0001$, $p=0.0031$ respectively. N-5; One-way ANOVA, Tukey's posthoc).
Conclusions: These data support the hypothesis that straight-, straight l-, and d,l-amphetamine produce differential DA and NE release in critical areas of the brain implicated in ADHD. The potential implications for selective prescribing for types of ADHD patients as well as side effect profiles of these neurobiological differences will be discussed.

**44. DOPAMINE MODULATION OF ACTION CONTROL IN A RODENT MODEL OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Joman Natsheh*[1], Michael Shiflett[2], Marwa Abdelaziz[2], Emaan Chaudhry[2], Samanthika Devalaraju[2], Delia Duran[2], Victor Lopez[2], Sydney Pacelli[2]

[1]Center for Molecular and Behavioral Neuroscience, Rutgers University, [2]Rutgers University

Background: Patients with Attention-Deficit/Hyperactivity Disorder display reward and motivational impairments. A potential mechanism that underlies these deficits might be impaired action control, which is the process by which voluntary actions are selected and executed based on prior reinforcement learning. 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. Studies suggest that brain regions responsible for action control as well as dopamine signaling within these regions show abnormalities in patients with ADHD. Accordingly, we propose that patients with ADHD exhibit an impairment in action control with biased reliance on the habit system at the expense of the goal-directed system. We previously showed that spontaneously hypertensive rats (SHR), a rat model of ADHD, show an impaired goal-directed behavior. This impairment was improved by injections of methylphenidate, the most commonly used psychostimulant in ADHD treatment.
Methods: In this study, we examined dopamine modulation of action control in SHR using an outcome devaluation paradigm. We tested 72 male adult (P49-P80) rats; 36 of which were SHR and 36 were Wistar-Kyoto rats (WKY), the normotensive control strain. Two behavioral experiments were conducted to study the effects of dopamine D1 receptor (D1R) and dopamine D2 receptor (D2R) agonists and antagonists on goal-directed behavior: SCH23390 (D1R-antagonist) and Quinpirole (D2R-agonist) in experiment #1, and SKF38393 (D1R-agonist) and

Raclopride (D2R-antagonist) in experiment #2. In both experiments, rats underwent 10 days of instrumental conditioning in which they separately acquired two distinct action-outcome contingencies. Responses on one lever were associated with delivery of grain pellets and with chocolate pellets on another lever. Rats underwent an outcome devaluation test prior to which one of the instrumental outcomes was devalued through specific satiety and rats were given an intraperitoneal injection of normal saline (as a control), or a dose of a dopaminergic drug. Goal-directed behavior was identified by higher response rate on the valued lever during the outcome devaluation test, while habitual behavior was identified by comparable responses on the valued and the devalued levers.

Results: In experiment #1, we found that stimulation of D2R using a D2R agonist or inhibition of D1R using a D1R antagonist restored goal-directed behavior in SHR that, under control conditions exhibit habitual behavior. In experiment #2, we found that stimulation of D1R using a D1R agonist or inhibition of D2R using a D2R antagonist did not improve behavior in SHR, who continued to respond habitually. All four drugs impaired goal-directed behavior in WKY that was previously intact following saline injection.

Conclusions: Our results indicate that the core behavioral deficit in ADHD might not be a consequence of dopamine hypofunction, but rather due to an imbalance between activation of D1R and D2R pathways that govern action control. Unraveling these mechanisms can broaden our understanding of the neural circuits underlying cognitive symptoms of ADHD. These findings might elucidate novel potential treatment approaches to create a balance between ADHD symptom relief and remediation of behavioral deficits.

45. THE ENDOCYTIC REGULATION OF AUTOPHAGY AND CELL SURVIVAL: PATHWAY INTERACTIONS FOR ADHD- AND AUTISM-RISK GENE SLC9A9

Jameson Patak*[1], Jonathon Hess[1], Yanli Zhang-James[1], Stephen Glatt[1], Stephen Faraone[1]

[1]SUNY Upstate Medical University

Background: Mutations in sodium hydrogen exchanger 9 (SLC9A9) have been implicated in ADHD and autism spectrum disorders. SLC9A9 regulates the endosome-recycling compartment through alkalinizing the endosomal lumen; although, it's broader biological functions have not been elucidated.

We set out to discover broader biological functions for SLC9A9 using co-expression analysis. We also confirm the most significant bioinformatic associations using an in vitro neuronal model.

Methods: We performed weighted gene co-expression network analysis (WGCNA) on human RNA-sequencing data from Allen Brain Atlas focusing on SLC9A9 co-expression modules in the pre- and postnatal hippocampus, cortex and amygdala. We use N2a cells as a neuronal model system and transfected them with SLC9A9 cDNA constructs using lipofectamine 2000. We assessed immunoblots of N2a protein lysate for various autophagic and cell survival pathway intermediates. In addition, we challenge N2a cells with chloroquine to assess their viability.

Results: Our SLC9A9 co-expression modules are enriched with mTOR and autophagic intermediates, as well as Bcl-2 pathway constituents. Our in vitro work demonstrates that SLC9A9 overexpression in N2a cells significantly decreases LC3-I to LC3-II conversion and significantly increases Bcl-2 levels. In addition, SLC9A9 increases phospho-AKT and phospho-mTOR levels, decreases LC3-II puncta formation and autophagic rate and provides resistance to drug treatments that typically result in cell death.

Conclusions: Our data suggests that SLC9A9 expression could be a signaling and ion-transport brake that effectively inhibits autophagic processes. When dysregulated, this has the potential to impact pruning and thus neuronal morphology and function. These results provide further insight into how SLC9A9 is impacting neuronal function and how it can, potentially, lead to psychiatric traits when dysregulated through mutations or copy number variants.

**46. REGIONAL BRAIN NETWORK ORGANIZATION DISTINGUISHES THE COMBINED AND INATTENTIVE SUBTYPES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

Jacqueline Saad*[1], Kristi Griffiths[2], Michael Kohn[3], Simon Clarke[3], Leanne Williams[4], Mayuresh Korgaonkar[2]

[1]The University of Sydney, [2]Brain Dynamics Centre, The Westmead Institute for Medical Research, The University of Sydney, [3]Centre for Research into Adolescents' Health, Westmead Hospital, [4]Stanford University

Background: Attention Deficit Hyperactivity Disorder (ADHD) is characterized clinically by hyperactive/impulsive and/or inattentive symptoms which determine diagnostic subtypes as Predominantly Hyperactive-Impulsive (ADHD-HI), Predominantly Inattentive (ADHD-I), and Combined (ADHD-C). Neuroanatomically though we do not yet know if these clinical subtypes reflect distinct aberrations in underlying brain organization.
Methods: We imaged 34 ADHD participants defined using DSM-IV criteria as ADHD-I (n= 16) or as ADHD-C (n=18) and 28 matched typically developing controls, aged 8-17 years, using high-resolution T1 MRI. To quantify neuroanatomical organization, we used graph theoretical analysis to assess properties of structural covariance between ADHD subtypes and controls (global network measures: path length, clustering coefficient, and regional network measures: nodal degree). As a context for interpreting network organization differences, we also quantified gray matter volume using voxel-based morphometry.
Results: Each ADHD subtype was distinguished by a different organizational profile of the degree to which specific regions were anatomically connected with other regions (i.e., in "nodal degree"). For ADHD-I (compared to both ADHD-C and controls) the nodal degree was higher in the hippocampus. ADHD-I also had a higher nodal degree in the supramarginal gyrus, calcarine sulcus, and superior occipital cortex compared to ADHD-C and in the amygdala compared to controls. By contrast, the nodal degree was higher in the cerebellum for ADHD-C compared to ADHD-I and in the anterior cingulate, middle frontal gyrus and putamen compared to controls. ADHD-C also had reduced nodal degree in the rolandic operculum and middle temporal pole compared to controls. These regional profiles were observed in the context of no differences in gray matter volume or global network organization.
Conclusions: Our results suggest that the clinical distinction between the Inattentive and Combined subtypes of ADHD may also be reflected in distinct aberrations in underlying brain organization.

**47. LISDEXAMFETAMINE TARGETS AMYGDALA MECHANISMS THAT UNDERLIE THE EMOTIONAL BIAS OF COGNITIVE CONTROL: RELATION TO CLINICAL IMPROVEMENT IN ADULTS WITH ADHD

Kurt Schulz*[1], Beth Krone[1], Lenard Adler[2], Anne-Claude Bedard[3], Juan Pedraza[1], Jeffrey Newcorn[4]

[1]Icahn School of Medicine at Mount Sinai, [2]NYU School of Medicine, [3]University of Toronto, [4]Mount Sinai Medical Center

Background: Prefrontal-limbic circuits that form the neural architecture for emotion to influence behavior have been implicated in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD), and represent a potentially important target of medication treatment that has not been substantively evaluated. This study tested the effect of the psychostimulant prodrug lisdexamfetamine dimesylate on amygdala activation and connectivity during the emotional bias of response execution and inhibition.
Methods: Twenty-five adults with ADHD were scanned twice with event-related functional magnetic resonance imaging while performing an emotional go/no-go task following three to four weeks of lisdexamfetamine treatment and three weeks off medication in a randomized, counterbalanced, hybrid crossover design. Drug, trial type, and face emotion (happy, sad, neutral) were included as within-subjects factors in repeated measures analyses of activation and connectivity.
Results: Lisdexamfetamine was associated with increased right amygdala activation and reduced psychophysiological interactions with the orbital aspect of left inferior frontal gyrus specifically for responses to sad faces compared to placebo, but there was no effect on the accuracy of response execution or inhibition. The relative gain in right amygdala activation in response to sad faces for lisdexamfetamine was correlated with a reduction in symptoms of ADHD.
Conclusions: Treatment with lisdexamfetamine potentiates affective encoding in amygdala, purportedly via catecholaminergic mechanisms, but functionally disconnects amygdala from inferior frontal regions that encode behavioral significance– resulting in reduced emotional bias of cognitive control. Pinpointing the neurophysiologic underpinnings of therapeutic improvement with lisdexamfetamine represents a first step in developing targeted approaches to treatment of ADHD.

48. SEARCHING FOR NEURAL BIOMARKERS OF THE RISK FOR PEDIATRIC MOOD DISORDERS: A CONTROLLED FMRI STUDY IN CHILDREN

Joseph Biederman*[1], Mai Uchida[2], Yuwen Hung[3], Caroline Kelberman[1], Schuyler Gaillard[3], John D. E. Gabrieli[3]

[1]Massachusetts General Hospital, [2]Massachusetts General Hospital & Harvard Medical School, [3]Massachusetts Institute of Technology

Background: The goal of this study was to identify neurobiological underpinning of childhood emotional dysregulation (ED), based on aggregate elevations on Anxiety/Depression, Attention Problems and Aggression Child Behavior Checklist subscales (AAA scores), which is significantly associated with current and future mood disorders and psychosocial dysfunction.
Methods: We collected neuroimaging data and psychometric assessments of total of 43 children (21 girls and 22 boys; mean age = 10.3 ± 2.4 years; AAA range = 155 – 257). We used the whole-brain voxel-wise method to analyze the Diffusion Tensor Imaging data; a non-parametric regression analysis for relations between AAA score and strength of anatomical connectivity. We then analyzed the combined DTI and resting-state fMRI to reveal task-free structural and functional brain connectivity underlying CBCL AAA profile.
Results: The CBCL-AAA profile can sensitively reveal altered structural and functional connectivity in the cingulate pathways. The diffusion-directed seeding approach successfully detected changes in long-range functionally connectivity, which the conventional anatomical

seeding approach was unable to show. Cingulum connectivity and PCC-anterior resting-state functional connectivity is related to the changes in emotional dysregulation profiles in children. Altered cingulum and PCC-anterior brain connectivity may manifest as a possible risk biomarker or a developmental precursor predictive of a potential clinical course toward mood disorders in children.
Conclusions: This is the first study to provide a neurobiological account at the whole-brain level for the CBCL emotion dysregulation profile. The findings of this study may contribute to clinical screening and early identification of pediatric mood disorders. The cingulum brain pathways may be targeted for future preventive effort.

49. OPEN BOARD

50. THERAPEUTIC RESPONSE AND SIDE-EFFECTS TO METHYLPHENIDATE IN ADHD: ROLE OF GENDER OF THE CHILD AND THE OBSERVER

Venkat Bhat*[1], Natalie Grizenko[2], Ridha Joober[2]

[1]University of Toronto, [2]McGill University

Background: Gender-based differences have been described in children with Attention Deficit Hyperactivity Disorder (ADHD). These gender-based differences have not been well characterized while taking into account the gender of the observer. This project aims to examine the role of the genders of the child and observer in TR in various observational settings (parent, teacher, laboratory, clinical).
Methods: 299 children (269-male, 30-female; average age 8.9±1.8) with ADHD underwent a two-week double-blind, placebo controlled randomized, cross-over clinical trial with Methylphenidate (MPH). Behavioral assessments included the Conner's Global Index from parents (CON-P), teachers (CON-T), clinicians (CGI, GPI), and measures including CPT and RASS. The difference scores between MPH and placebo was calculated for each measure as an index of treatment response with MPH and the various TR measures were examined using a univariate ANCOVA correcting for any significant baseline covariates. Finally, the significant SE with MPH were compared for gender-based differences of parent observer using a t test.
Results: As expected, significant TR was noted in all measures of behaviors ($P<0.00$). During the baseline week, the ANCOVA analysis for teachers yielded a significant interaction based on the gender of the teacher and child, and the interaction effect was seen in both dimensions of CON-T ($p<0.05$). For the TR ANCOVA analysis, a significant interaction based on the gender of the teacher and child was noted only for the Restless Impulsive dimension. The ANCOVA analysis for parents did not note any differences with TR and observed significant differences based on the child's gender at baseline ($p<0.05$). The other observations (CPT, RASS, CGI, GPI) did not show any significant differences on ANCOVA. Finally, the SE of decreased appetite is noted on the t test as a more frequent observation among mothers during TR.
Conclusions: The TR with MPH was consistently observed in all observation settings suggesting that MPH improved outcomes. The observation that teachers had gender-based baseline interactions unlike parents suggests that there are differences in symptom assessment between parents and teachers at baseline. Further, the observation that teachers note a gender-based treatment differences with bigger improvement for male children while parents do not suggests that TR is observed differently based on requirements of settings. The fact that no gender-based changes are seen on RASS, CPT and by clinicians suggests that parents and

teachers have gender-based expectations of child behavior & TR. This is further supported by the result that female parents note greater decreased appetite as a SE as compared to male parents.

51. THERAPEUTIC RESPONSE AND SIDE-EFFECTS IN CHILDREN WITH ADHD: ROLE OF OBSERVATION SETTING

Venkat Bhat*[1], Natalie Grizenko[2], Ridha Joober[2]

[1]University of Toronto, [2]McGill University

Background: Information obtained from parents and teachers is used to initiate stimulant treatments and further titration to achieve optimal therapeutic response (TR) and minimal side effects (SE) in ADHD. This study aims to examine correlations in TR obtained in various observation settings (parent, teacher, laboratory, clinical).
Methods: 526 children (420-male, 106-female) with ADHD underwent a two-week double-blind, placebo controlled randomized, cross-over clinical trial with Methylphenidate (MPH). Behavioral assessments included the Conner's Global Index from parents (CON-P), teachers (CON-T), the clinical global impression for improvement assessed by clinicians (CGI), and direct observations of child behaviors in a structured classroom like environment (RASS), and cognitive tests evaluating continuous attention (CPT). The difference scores between MPH and placebo weeks was calculated to reflect TR. Side effects (SE) and other pertinent variables were used as covariates using a bivariate partial correlation analysis of TR interrelationship in the various observation settings.
Results: Insomnia, talking less, decreased appetite, stomachaches and headaches were the SE noted with MPH ($p<0.05$) compared to placebo, and they were used as covariates in the bivariate correlation analysis. At baseline, all assessments showed significant correlations ($p<0.00$). At baseline, the correlation between parents and teachers was mainly in the RI dimension and among boys. However, with TR, no correlation was noted between parents and teachers and other observation settings. Further, CPT, RASS, CGI were significantly correlated among each other ($p<0.00$), and GPI was significantly correlated with all observations ($P<0.00$). Finally, the effect size of the observed correlations was modest ($r2 = 0.05$ with TR, 0. 1 with baseline, 0.2 with RASS and CPT and, 0.4 with CGI and GPI).
Conclusions: The TR with MPH was consistently observed in all observation settings suggesting that MPH improved outcomes. While baseline results are correlated among all observers, TR shows variable correlation with no correlation between parents/teachers and CPT/RASS. The results suggest that there is greater heterogeneity in TR as compared to at baseline by parents and teachers. However, CPT, RASS and CGI have correlations suggesting common elements in improvement. The observed effect sizes suggest a complex interplay of many factors. The results firmly support the need to synthesize information from many sources.

52. THERAPEUTIC RESPONSE AND SIDE-EFFECTS TO METHYLPHENIDATE IN ADHD: ROLE OF CO-MORBIDITY

Venkat Bhat*[1], Natalie Grizenko[2], Ridha Joober[2]

[1]University of Toronto, [2]McGill University

Background: Population studies suggest that ADHD has high rates of comorbidity with other disorders including, oppositional defiant disorder, conduct disorder and anxiety disorders. Further, comorbidity could impact therapeutic response (TR) and side effects (SE) seen in

various observation settings when children with ADHD are on stimulant medications. This project aims to examine the impact of comorbidity on TR noted in various observation settings (parent, teacher, laboratory, clinical).
Methods: 526 children (420-male, 106-female) underwent a two-week double-blind, placebo controlled randomized, cross-over clinical trial with Methylphenidate (MPH). Behavioral assessments included the Conner's Global Index from parents (CON-P), teachers (CON-T), clinicians (CGI, GPI), and measures including CPT and RASS. The difference scores between MPH and placebo weeks was calculated to arrive at an index of TR. Following examination for significant demographic variables which were used as covariates, the CON-T, CON-P, RASS, CPT, CGI, and GPI were examined for differences based on comorbidity using an independent samples t test. Finally, the significant side-effects were contrasted by comorbidity using an independent sample t-test.
Results: Children ADHD had an average age of 8.9 (±1.8) and children with comorbidity had lower family incomes, worse scores on CBCL, more Inattentive and Hyperactive features, and a higher incidence of mothers who had smoked during pregnancy (MSDP). Among comorbidities, oppositional defiant disorder (ODD) was the most common comorbidity followed by anxiety disorders. The CON-T was not different at baseline but TR was poorer for total score and subscores ($p<0.00$) in the presence of comorbidity ($p<0.00$). Parents (CON-P) noted significant differences for total score and scores at baseline in the presence of comorbidity($p<0.00$), but not with TR . Among comorbidities, ODD was the principal contributor to the differences noted with CON-P and CON-T. No significant differences were noted on RASS, CPT, CGI, and GPI based on comorbidity at baseline or on treatment. Among SE, insomnia was significantly more common in the presence of comorbidity.
Conclusions: Presence of comorbidity was associated with lower family incomes, higher MSDP and more severe clinical features both of which have been associated in previous studies. Teachers did not note baseline differences but noted differences with TR and parents noted baseline differences but no differences with TR. Further the observation that teachers and parents note the difference mainly for ODD but not the other major comorbidities suggests that ODD subtype leads to differential assessment of TR. The lack of response differences noted with CPT, RASS and CGI-C suggests that comorbidities might bias parent and teacher assessments. Finally, higher insomnia at baseline could contribute to smaller improvements with treatment in the presence of comorbidity.

53. SINGLE- AND MULTIPLE-DOSE PHARMACOKINETICS OF KP415, A NOVEL D-METHYLPHENIDATE PRODUCT CONTAINING A PRODRUG OF D-METHYLPHENIDATE, IN HEALTHY VOLUNTEERS

Rene Braeckman[1], Sven Guenther[1], Travis Mickle[1], Andrew Barrett*[1], Adam Smith[1], Kathryn Roupe[2], Michael Nutt[2], Cynthia Zamora[2]

[1]KemPharm, Inc., [2]Worldwide Clinical Trials

Background: KP415 is an investigational ADHD product containing both d-methylphenidate (d-MPH) and a novel prodrug of d-MPH. Preliminary pharmacokinetic data indicated that the prodrug produces a gradual, extended-release of d-MPH. Following a single KP415 dose, initial d-MPH exposure during the first several hours is governed by d-MPH API and subsequent sustained d-MPH exposure primarily by prodrug conversion to d-MPH. The primary objective of this study was to assess the single- and multiple-dose pharmacokinetics of d-MPH following multiple doses of different ratios of d-MPH API and prodrug. Such data were informative for selecting a d-MPH/prodrug ratio most appropriate for a once-daily d-MPH product designed to provide rapid and durable efficacy throughout the day.

Methods: This was a Phase 1, open-label, multiple-dose, 4-treatment, randomized, parallel pharmacokinetic study evaluating oral solutions with different ratios of d-MPH API and prodrug compared with Concerta®, in healthy adult volunteers (N=48) under fasted conditions. Oral solutions were administered containing 8/64 mg, 12/56 mg, and 16/48 mg of d-MPH API/prodrug, corresponding to d-MPH:prodrug ratios (expressed in wt-%:wt-% of total d-MPH dose) of approximately 20%:80%, 30%:70%, and 40%:60%. The total d-MPH equivalent dose was 40 mg. The fourth treatment was Concerta, 54 mg tablets. Eligible subjects (12 per treatment group) were randomized to receive multiple doses of d-MPH API and prodrug (administered separately in 10-mL oral solutions), or one Concerta tablet each day for 7 days. Blood samples for pharmacokinetic analysis were collected during the multiple-dose regimen and safety assessments were performed.
Results: Following all treatments with d-MPH API/prodrug, d-MPH plasma concentrations increased rapidly and exhibited a single peak at approximately 1.5 to 2 hours after Dose 1 and Dose 7, followed by a gradual decline in d-MPH concentrations over the remainder of the dosing interval. Peak plasma concentrations (Cmax), primarily determined by d-MPH API in each combination, increased dose-dependently across doses of 8/64 mg (15.5 ng/mL), 12/56 mg (20.9 ng/mL), and 16/48 mg (23.8 ng/mL). After both Dose 1 and Dose 7, initial onset of d-MPH plasma concentrations was faster and higher following treatments with d-MPH API/prodrug through at least 4.5 hours postdose when compared with Concerta. Overall d-MPH exposure during the 24-hour dosing interval (AUC0-24) was comparable across the three dose combinations (187.0 – 207.7 h*ng/mL). When compared to Concerta, mean d-MPH plasma concentrations were higher following treatments with d-MPH API/prodrug at 24 hours after Dose 1 as were all subsequent predose d-MPH concentrations on Days 3 to 7. Across the three dose combinations, accumulation of d-MPH at steady-state (Dose 7 vs. Dose 1) ranged from 20-33% for Cmax, 18-31% for Cmin, and 25-34% for AUC0-24. For all three dose combinations, exposure to intact prodrug peaked at approximately 2 hours postdose and was largely eliminated by 24 hours with little or no accumulation of intact prodrug after 7 doses. Adverse events after all treatments were typical of stimulants.
Conclusions: Based on a desired product profile that demonstrates rapid onset and sustained delivery of d-MPH at steady-state, with low levels of accumulation for both d-MPH and intact prodrug, a d-MPH dose ratio of 30% d-MPH API to 70% prodrug (corresponding to the 12/56 mg d-MPH API/prodrug combination in this study) was selected for further clinical development of KP415.

54. RELATIONSHIPS BETWEEN EXECUTIVE FUNCTION IMPROVEMENT AND ADHD SYMPTOM IMPROVEMENT WITH LISDEXAMFETAMINE DIMESYLATE IN ADULTS WITH ADHD AND EXECUTIVE FUNCTION DEFICITS: A POST HOC ANALYSIS

Thomas Brown*[1], Yi Chen[2], Victor Otcheretko[2], Brigitte Robertson[2]

[1]Keck School of Medicine of University of Southern California, [2]Shire

Background: Executive function (EF) deficits are not generally considered synonymous with attention-deficit/hyperactivity disorder (ADHD), and while ADHD symptoms and EF deficits may overlap, EF deficits and impairments go beyond the Diagnostic and Statistical Manual for Mental Disorders (DSM) criteria. Therefore, it is important to assess the impact of stimulants on the EF deficits and impairments associated with ADHD using measures like the Behavior Rating Inventory of Executive Function–Adult version (BRIEF-A), which captures deficits not accounted for by the ADHD Rating Scale (ADHD-RS) alone. In adults with DSM-defined ADHD and clinically-relevant EF deficits (indexed by self-report BRIEF-A Global Executive

Composite [GEC] T-scores ≥65), lisdexamfetamine dimesylate (LDX) significantly improved EF and reduced ADHD symptoms (measured by ADHD-RS with Adult Prompts Total Score [ADHD-RS-AP-TS]). While evidence suggests stimulants improve ADHD symptoms and EF deficits in adults with ADHD, the relationships between improvement in ADHD symptoms and EF deficits following stimulant treatment have not been studied. We conducted post hoc analyses examining these relationships following LDX treatment.

Methods: These post hoc analyses used data from a 10-week randomized, double-blind, placebo (PBO)–controlled study of dose-optimized LDX (30–70 mg) that enrolled adults with ADHD and EF deficits. Efficacy endpoints included change from baseline at week 10/early termination (ET) in self-report BRIEF-A GEC T-score (primary) and ADHD-RS-AP-TS (secondary). Bidirectional relationships between ADHD symptom and EF changes from baseline at week 10/ET were examined with recursive path analyses involving treatment (LDX vs PBO) and mediators and outcomes (self-report BRIEF-A GEC T-score and ADHD-RS-AP-TS); baseline mediator and outcome values were included in the model.

Results: The mediation proportion (indirect treatment effect/total treatment effect) of the self-report BRIEF-A GEC T-score change from baseline at week 10/ET on ADHD-RS-AP-TS change from baseline at week 10/ET was 0.62 (indirect treatment effect coefficient [95% CI], –6.85 [–9.83, –3.86]; total treatment effect coefficient [95% CI], –11.12 [–14.88, –7.37]) and for ADHD-RS-AP-TS change from baseline at week 10/ET on self-report BRIEF-A GEC T-score change from baseline at week 10/ET was 0.93 (indirect treatment effect coefficient [95% CI], –10.34 [–14.11, –6.57]; total treatment effect coefficient [95% CI], –11.18 [–15.80, –6.55]). This suggests 62% of the LDX treatment effect on ADHD symptoms in the population studied could be mediated by improvement in EF and 93% of the LDX treatment effect on BRIEF-A GEC T-score could be mediated by improvement in ADHD symptoms.

Conclusions: While these data suggest improvements in ADHD symptoms, measured by ADHD-RS-AP-TS, and EF deficits, measured by BRIEF-A GEC T-score, following LDX treatment are interdependent, it is advantageous to use measures like the BRIEF-A to assess the impact of stimulants on the wide range of EF deficits associated with ADHD that are not captured by the ADHD-RS-AP alone.

55. EFFICACY AND SAFETY OF SPN-810 (EXTENDED-RELEASE MOLINDONE) TO TREAT IMPULSIVE AGGRESSION IN CHILDREN BEING OPTIMALLY TREATED FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: PHASE 2B AND OPEN-LABEL EXTENSION RESULTS

Gianpiera Ceresoli-Borroni*[1], Toyin Adewole[1], Tesfaye Liranso[1], Robert Findling[2]

[1]Supernus Pharmaceuticals, Inc., [2]Kennedy Krieger Institute/Johns Hopkins University

Background: SPN-810 (extended-release molindone) is a potent antagonist for the dopamine D2 and serotonin 5-HT2B receptors that is in development for treatment of impulsive aggression (IA) in children being optimally treated for attention-deficit/hyperactivity disorder (ADHD). Here we report results of a Phase 2b study and open-label extension (OLE).

Methods: Following a 3-week lead-in phase, patients were enrolled in a 39-day, Phase 2b, randomized, double-blind (DB), placebo-controlled, parallel-group, dose-ranging study. Key inclusion criteria for the DB study included age 6-12 years; confirmed diagnosis of ADHD; Retrospective-Modified Overt Aggression Scale (R-MOAS) score ≥20 after a 3-week, open-label, stimulant-optimization period; and Vitiello Aggression Scale score from -2 to -5 to screen for children with impulsive aggression. In addition to the optimized dose of ADHD medication, patients were randomized to treatment with placebo or one of three daily doses of SPN-810 stratified by weight (<30/≥30 kg): 12/18 mg (low dose), 24/36 mg (medium dose),

or 36/54 mg (high dose). Patients who completed the DB study were enrolled in a 6-month OLE in which SPN-810 doses were adjusted according to clinical response after blinded conversion to 18 mg (<30 kg) or 36 mg (≥30 kg), regardless of DB randomization. Endpoints presented include change from baseline in R-MOAS score to gauge IA, change from baseline in Clinical Global Impression (CGI) ratings, and adverse event (AE) occurrence. DB endpoints are presented by dose group; OLE endpoints are presented as a combined dose group.
Results: A total of 121 patients (placebo, n=31; low dose, n=29; medium dose, n=30; high dose, n=31) were randomized in the DB study, and 95 (78.5%) completed it; 78 patients (64.5% of DB patients) entered the OLE, and 52 (66.7%) completed it. A total of 118 patients (97.5%) were included in the DB intent-to-treat population. In the DB study, median change from baseline to end-of-treatment in R-MOAS scores were: placebo, -21; low dose, -32 (P=0.03 vs. placebo); medium dose, -29 (P=0.02 vs. placebo); and high dose, -21 (P=0.74 vs. placebo); indicating a nonlinear dose-response profile. In the OLE, median R-MOAS change from DB baseline to OLE end-of-study (EOS) was -27 (P<0.05) and median R-MOAS change from OLE baseline to OLE EOS was 2 (P=not significant), indicating improvement vs. DB baseline and stable effect vs. OLE baseline. In both the DB study and the OLE, CGI results (Severity and Improvement) were consistent with R-MOAS findings. In the DB study, the most common AEs with SPN-810 use were headache (10%), sedation (9%), and increased appetite (8%). In the OLE, the most common AEs with SPN-810 use were sedation (12%), weight gain (10%), increased appetite (9%), and somnolence (5%).
Conclusions: Improvements in IA behavior were achieved with SPN-810 treatment in the DB study, and were sustained during the OLE. SPN-810 was generally well tolerated, and AEs were consistent with the types of events expected in children receiving low-dose SPN-810 added to ADHD medication.[1]

1. Stocks et al. J Child Adolesc Psychopharmacol. 2012;22:102-11.

56. A RANDOMIZED, PLACEBO-CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF SHP465 MIXED AMPHETAMINE SALTS EXTENDED-RELEASE IN CHILDREN AND ADOLESCENTS WITH ADHD: EXPLORATORY ANALYSES BY AGE GROUP

Ann Childress*[1], Ming Yu[2], Brian Yan[2], Brigitte Robertson[2]

[1]Center for Psychiatry and Behavioral Medicine, Inc., [2]Shire

Background: To evaluate the efficacy, tolerability, and safety of SHP465 mixed amphetamine salts (MAS) extended-release by age group in a pediatric population of individuals with ADHD.
Methods: This randomized, double-blind, placebo (PBO)-controlled, dose-optimization study enrolled children (6–12 years old) and adolescents (13–17 years old) with DSM-IV-TR-defined ADHD and baseline ADHD Rating Scale IV (ADHD-RS-IV) total scores ≥28. Participants were randomized 1:1 to SHP465 MAS (Week 1: 12.5 mg; Week 2: titrated to 25 mg based on efficacy, safety, and tolerability; Weeks 3–4: final titrated dose [12.5 or 25 mg] maintained) or PBO. The prespecified primary (ADHD-RS-IV total score change from baseline to Week 4) and key secondary (Clinical Global Impressions–Improvement [CGI-I] score at Week 4) endpoints were assessed in the full analysis set (FAS) using linear mixed-effects models for repeated measures. Safety and tolerability, including treatment-emergent adverse events (TEAEs) and vital sign changes, were examined descriptively in the safety set. These

exploratory analyses examined efficacy, safety, and tolerability endpoints independently in children and adolescents.

Results: The FAS included 101 children (PBO, n=50; SHP465 MAS, n=51) and 156 adolescents (PBO, n=79; SHP465 MAS, n=77); the safety set included 106 children (PBO, n=52; SHP465 MAS, n=54) and 157 adolescents (PBO, n=79; SHP465 MAS, n=78). The least squares (LS) mean (95% CI) ADHD-RS-IV total score change from baseline to Week 4 favored SHP465 MAS over PBO in children (–21.8 [–25.5, –18.1] vs –9.8 [–13.6, –6.1]; effect size=0.93; nominal P<0.001) and adolescents (–20.3 [–23.1, –17.5] vs –11.6 [–14.3, –8.8]; effect size=0.72; nominal P<0.001). The LS mean (95% CI) CGI-I score at Week 4 (lower scores indicate improvement) also favored SHP465 MAS over PBO in children (2.2 [1.9, 2.6] vs 3.1 [2.7, 3.4]; effect size=0.70; nominal P<0.001) and adolescents (2.2 [1.9, 2.4] vs 2.9 [2.6, 3.1]; effect size=0.62; nominal P<0.001). The frequency of TEAEs was 77.8% (42/54) with SHP465 MAS and 46.2% (24/52) with PBO in children and 60.3% (47/78) with SHP465 MAS and 46.8% (37/79) with PBO in adolescents. The most frequently reported TEAE (SHP465 MAS vs PBO) was decreased appetite in both children (42.6% vs 7.7%) and adolescents (21.8% vs 6.3%). Mean ± SD changes from baseline at the final on-treatment assessment (SHP465 MAS and PBO, respectively) were observed for pulse (children: 7.6±12.50 and 2.8±10.19 bpm; adolescents: 4.5±11.18 and –0.7±11.00 bpm), systolic blood pressure (children: 4.9±9.13 and 1.3±7.52 mmHg; adolescents: 3.0±9.15 and 2.6±9.41 mmHg), and diastolic blood pressure (children: 4.7±7.72 and –0.9±7.79 mmHg; adolescents: 3.6±8.57 and 1.4±7.12 mmHg).

Conclusions: Improvements in ADHD symptoms and global functioning favored SHP465 MAS over PBO in both children and adolescents with ADHD. While the frequency of some adverse events was higher in children, possibly associated with higher SHP465 MAS exposure, the overall safety and tolerability profile of SHP465 MAS in both age groups was generally consistent with the known profiles of other stimulants.

57. EARLY-ONSET EFFICACY AND SAFETY PILOT STUDY OF AMPHETAMINE EXTENDED-RELEASE ORAL SUSPENSION IN THE TREATMENT OF CHILDREN WITH ADHD

Ann Childress*[1], Sally A. Berry[2], Antonio Pardo[2], Heidi W. Belden[2]

[1]Center for Psychiatry and Behavioral Medicine, Inc., [2]Tris Pharma, Inc.

Background: The efficacy and safety of an amphetamine extended release oral suspension (AMPH EROS) for the treatment of children ages 6 to 12 has been established in a Phase 3 placebo-controlled laboratory classroom study with results showing an onset of action of 1 hour and a duration of action to 13 hours post-dose.2 This double-blind, randomized, two-period, two-treatment, crossover study was designed primarily to demonstrate AMPH EROS had an onset of action as early as 30 minutes post-dose. To date, an ER amphetamine with an onset of action of 30 minutes after dosing has not been available. This unique characteristic provides healthcare professionals with an amphetamine-based treatment option to cover ADHD symptomatology through both the early hours of the day, when parents and caregivers often struggle to get their children with ADHD through the morning routine, and into the evening homework hours.

Methods: Male and female children aged 6 to 12 years diagnosed with ADHD and with an ADHD-Rating Scale-5 (ADHD-RS-5) score at screening ≥ 90th percentile for sex and age were enrolled. A daily dose between 5 and 20 mg of AMPH EROS was determined for each subject during an open-label phase by the investigator, and was based on history of medication treatment, adequate symptom control, and tolerability. Subjects were randomized to receive

either AMPH EROS or placebo in a DB laboratory classroom session, and then crossed over to receive the opposite treatment in a second classroom session 6 days later. Dosing in the DB phase was fixed at 15 mg, 17.5 mg, or 20 mg. Drug efficacy was assessed prior to dosing and at 30 minutes and 3 hours post-dose using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale. Safety was assessed measuring vital signs and adverse events.
Results: At 30 minutes and 3 hours post-dose, the change from pre-dose SKAMP-Combined scores for AMPH EROS compared to placebo were statistically significant, with 8.6 and 17.2 points difference in the SKAMP-Combined score ($p=0.01$, $p = 0.0002$), respectively. The effect size for AMPH EROS at the 30 minute and 3 hour post-dose time points were 0.95 and 1.57, respectively. Adverse events (>10%) reported during the open-label phase included upper respiratory tract infection, fatigue, abdominal pain upper, headache, decreased appetite, and affect lability.
Conclusions: AMPH EROS was effective in reducing symptoms of ADHD at 30 minutes and 3 hours post-dose. Adverse effects reported were mild or moderate in severity and consistent with those of other extended-release amphetamines.

58. EFFICACY, SAFETY, AND TOLERABILITY OF AN EXTENDED-RELEASE, ORALLY DISINTEGRATING METHYLPHENIDATE TABLET IN CHILDREN 6–12 YEARS OF AGE WITH ADHD: OPEN-LABEL, DOSE-OPTIMIZATION PERIOD OUTCOMES

Ann Childress*[1], Scott H. Kollins[2], Andrew J. Cutler[3], Andrea Marraffino[4], Carolyn R. Sykes[5]

[1]Center for Psychiatry and Behavioral Medicine, Inc., [2]Duke University, [3]Meridien Research, [4]Florida Clinical Research Center, LLC, [5]Neos Therapeutics, Inc.

Background: A once-daily, extended-release, orally disintegrating tablet (XR-ODT) formulation of methylphenidate (MPH) was recently approved by the US Food and Drug Administration for the treatment of attention deficit/hyperactivity disorder (ADHD) in patients 6 to 17 years of age. In a randomized, multicenter, double-blind, placebo-controlled, parallel-group laboratory classroom study, MPH XR-ODT significantly improved ADHD symptoms vs placebo and was well tolerated in children 6 to 12 years of age with ADHD. In this study, the MPH XR-ODT was titrated to an optimized dose (20 mg to 60 mg) during a 4-week open-label period and the optimized dose was maintained for 1 week prior to randomization. The objective of this analysis is to examine the efficacy and safety of MPH XR-ODT during the open-label, 5-week dose-optimization/stabilization (DOS) period.
Methods: Children aged 6 to 12 years meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision criteria for ADHD and who had a positive response to a stable dose of MPH for 1 month prior to screening were enrolled. ADHD diagnosis was confirmed with the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version. During the 4-week dose optimization period (visits 2–5), the dose could be increased in 10- to 20-mg increments until an optimal dose or until a maximum dose of 60 mg was reached. Participants stayed on the optimized dose for 1 week (dose stabilization period, visit 6) before the randomized part of the study began. During the DOS period, participants were evaluated for safety, tolerability, and efficacy to determine the optimal dose. Assessments of efficacy during the DOS period included the ADHD Rating Scale-IV (ADHD-RS-IV) and Clinical Global Impressions-Improvement (CGI-I) ratings.
Results: A total of 87 participants were enrolled; 85 completed the dose-optimization period, 83 completed the dose-stabilization period, and 82 were included in the full analysis set (ie, all randomized participants who had ≥1 postdose efficacy assessment during the classroom testing

session). Of the 87 enrolled participants, 24.1% had inattentive type ADHD, 1.1% were hyperactive/impulsive, and 74.7% had combined type ADHD. The final optimized dose was 20 mg for 12.6% (11/87) of participants, 30 mg for 24.1% (21/87) of participants, 40 mg for 27.6% (24/87) of participants, and 60 mg for 33.3% (29/87) of participants. The mean ± standard deviation (SD) dose of once-daily MPH XR-ODT during this period was 34.3±9.06 mg. Changes in CGI-I scores during the DOS period reflected the ADHD symptom improvement with treatment (mean ± SD: 3.1±1.06 at visit 3 to 1.7±0.56 at visit 6 [end DOS period]). The mean ± SD change from baseline in ADHD-RS-IV at the end of the DOS period for participants who were eventually randomized to placebo or MPH XR-ODT was −21.5±8.96 and −19.8±8.14, respectively. Treatment-emergent adverse events (TEAEs) were reported by 80.5% (70/87) of patients during the DOS period; 1 TEAE resulted in discontinuation and there were no serious TEAEs. The most common TEAEs during the DOS period (≥10% of patients) included decreased appetite, upper abdominal pain, headache, insomnia, and upper respiratory tract infection; all were considered mild or moderate.

Conclusions: Open-label MPH XR-ODT treatment was associated with a reduction in ADHD symptoms over the course of the 5-week DOS period and was generally well tolerated in children with ADHD.

59. APPROACHED TO SHARE OR SELL YOUR MEDS? COLLEGE STUDENTS WITH ADHD AND SUBSTANCE-TOLERANT SOCIAL ENVIRONMENTS

Montaya Dawkins*[1], Heather Joseph[2], Heidi Kipp[1], Engster Stacey[3], Rachel Lindstrom[1], Seth Harty[4], Bridget Newman[5], Srihari Bangalor[6], Brooke Molina[7]

[1]University of Pittsburgh Medical Center, Western Psychiatric Institute & Clinic, [2]University of Pittsburgh School of Medicine, [3]University of Pittsburgh Medical Center, [4]University of Canterbury, [5]RTI International, [6]Roseville Medical Center, [7]University of Pittsburgh

Background: Misuse of prescription stimulant medication has increased among college students. A number of studies have investigated non-prescribed stimulant medication use by college students, but we know very little about the characteristics of college students with ADHD (Attention-Deficit/Hyperactivity Disorder) who have stimulant prescriptions and may be vulnerable to diverting (sharing or selling) their stimulant medication. Substance-tolerant social environments may promote stimulant diversion. The aim of this study was to test this hypothesis in a primary care-recruited sample of college students receiving stimulant prescriptions for ADHD.

Methods: Participants were young adults treated for ADHD with a stimulant by a primary care provider and who were enrolled in college (N=114, Mage=20.4, SD=1.6). Approximately half (53%; 60/114) were male, and 95.6% (109/114) were White or Caucasian. Most (68%; 77/114) were enrolled in a 4-year college or university. All completed an online survey about their utilization, including diversion, of stimulant medication and a battery of questions about domains hypothesized to relate to propensity to share, sell, trade, or loan stimulant medication. For the current report, measures reviewed were: report of being approached to divert, marijuana use, other illicit substance use, binge drinking (alcohol), stimulant medication misuse, negative consequences from using drugs or alcohol, and perceived peer misuse of stimulant medication.

Results: Stimulant diversion was infrequent, but many (52.63%) were approached to sell or share their stimulant medication in the past year. In comparison to those not approached, these participants were not more likely to use their stimulant medication more than prescribed, t(112)=-1.651, p=.101, misuse prescription medications (i.e. valium, tranquillizers, cough medicine) t(112)= -.770, p=.443, or use illicit drugs (e.g., heroin), t(112)= -.846, p=-.399.

However, they reported more frequent binge drinking, t(112)=-3.725, p=.000 and marijuana use, t(112)= -4.794, p=.000, more negative consequences from using drugs and alcohol, t(112)= -4.476, p=0.05, and higher likelihood of using stimulants in combination with other drugs or alcohol t(112)= -3.310, p=.001. They were also more likely to have peers who misused stimulant medication for studying t(112)= -5.390, p=.000, and partying t(112)= -5.014, p=.000.

Conclusions: College students who use substances such as marijuana and alcohol, combine their stimulants with substances, and are in social environments that tolerate stimulant misuse are likely to be approached to sell or share their stimulant medication. Primary care providers should consider these high-risk characteristics when treating their young adult patients with ADHD. Reflected in our ongoing work, these results should also be incorporated in the development and testing of interventions to prevent or decrease stimulant diversion by young adults with ADHD.

60. EXECUTIVE FUNCTIONING IN EVERYDAY LIFE IN EMERGING ADULTS WITH ADHD

Ronna Fried*[1], Robert Roth[2], Peter Isquith[3], Maura Fitzgerald[4], Heidi Boland[4], Joseph Biederman[1]

[1]Massachusetts General Hospital & Harvard Medical School, [2]Geisel School of Medicine at Dartmouth, [3]Harvard Medical School & Geisel School of Medicine at Dartmouth, [4]Massachusetts General Hospital

Background: Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder that persists into adulthood for many individuals. Emerging adulthood, the period between 18 and 29 years of age, has been identified as a distinct developmental stage. Importantly, neurodevelopmental changes continue to take place from late adolescence into this stage, including in the prefrontal cortex, a brain region intimately involved in executive functions. There has been relatively little research focused on cognition in emerging adults with ADHD, however, and what has been done is mainly correlational and focused on college student samples. In the present study, we examined self-rated executive functioning in a large sample of emerging adults with ADHD.

Methods: Participants included 55 unmedicated emerging adults with ADHD (mean age = 24.4, SD = 2.9) and 55 healthy comparison (HC) subjects (mean age = 24.4, SD = 2.8) matched for age and gender (45.5% female). Patients were excluded if they had a history of bipolar disorder or conduct disorder, or current major depression, anxiety disorder, OCD, or alcohol or substance use disorder. Participants completed the Behavior Rating Inventory of Executive Function – Adult version (BRIEF-A), comprised of nine theoretically and empirically derived scales, assessing executive functioning in everyday life over the past month. Most patients (n = 49) also completed the Adult ADHD Self Report Scale (ASRS), which indicated that 69.4% were of the combined subtype.

Results: MANOVA revealed that the ADHD group endorsed significantly greater difficulty with executive functions overall than the HC group ($p. < 001$, $\eta 2p = .53$) with greater difficulty on 8 of 9 scales ($\eta 2p = .06$ to $.45$). The largest effect sizes were seen in working memory, planning/organization, and self-monitoring of performance on tasks. Small group differences in education did not alter the pattern of results. Greater ADHD symptom severity was associated with worse scores on all BRIEF-A scales.

Conclusions: Emerging adults with ADHD endorse considerable difficulty with executive functions in their everyday lives. Further research will be needed to determine whether

executive dysfunction contributes to the myriad of problems noted in this population including difficulties with interpersonal relationships, academic and occupational functioning, increased likelihood of engaging in risky sexual behavior, and alcohol and substance use.

61. MODELING THE TRAJECTORY OF ADHD SYMPTOMS THROUGHOUT THE DAY IN CHILDREN TREATED WITH PLACEBO IN A LABORATORY CLASSROOM SETTING STUDY

Roberto Gomeni*[1], Seth Hopkins[2], Antony Loebel[2], Kenneth Koblan[2]

[1]PharmacoMetrica, [2]Sunovion Pharmaceuticals Inc.

Background: The laboratory classroom study design is intended to evaluate the time course (onset and duration) of drug effects on ADHD symptoms throughout the day. Dasotraline is a novel dopamine and norepinephrine reuptake inhibitor which achieves stable plasma concentrations over 24 hours. Dasotraline treatment was evaluated in children with ADHD in a randomized, double-blind laboratory classroom study (NCT02734693). However, in contrast to prior classroom studies, a classroom day was conducted prior to randomization as a pre-treatment baseline (Day 1). The effects of treatment were analyzed at endpoint (Day 15) following 14 days of treatment with placebo or dasotraline (4 or 6 mg/day). The objective of this analysis was to characterize trajectory of SKAMP scores throughout the day in unmedicated children with ADHD, and to characterize the response to 14 days of placebo treatment on the primary outcome measure, the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) scale.

Methods: The study enrolled children ages 6-12 years who met DSM-5 criteria for a primary diagnosis of ADHD with an ADHD Rating Scale Version IV total score ≥26. The trajectory of SKAMP scores throughout the day was modeled using an indirect response model with a time-varying effect in patients treated with placebo (N=56) using a beta regression modeling approach together with an evaluation of the inter-individual variability

Results: The results of the analysis indicate that placebo treatment was associated with large inter-individual variability in SKAMP trajectories. However, the pattern of SKAMP scores over the course of the classroom day were remarkably stable between the 2 assessment time-points (2 weeks apart) within individuals. The deterioration in ADHD symptoms over the first 6 hours in the classroom day reached a maximum at approximately 2 pm. Both the average SKAMP score throughout the day, and the worsening over the course of the day, were influenced by covariates of baseline SKAMP score and demographic covariates (age, race, sex).

Conclusions: The indirect-response longitudinal model provided a good description of the variability in the trajectory of SKAMP scores in patients treated with placebo on both Day 1 and Day 15 of study treatment. These results provide a quantitative description of how placebo-related ADHD symptoms change over the course of the day and demonstrate for the first time a remarkable stability of (intra-individual) SKAMP scores at baseline (Day 1) versus endpoint (Day 15) among children with ADHD treated with placebo in the classroom setting.

Sponsored by Sunovion Pharmaceuticals, Inc.

62. MODELING EXPOSURE-RESPONSE OF DASOTRALINE ON ADHD SYMPTOMS THROUGHOUT THE DAY IN CHILDREN WITH ADHD IN A LABORATORY CLASSROOM SETTING STUDY

Seth Hopkins*[1], Roberto Gomeni[2], Antony Loebel[1], Kenneth Koblan[1]

[1]Sunovion Pharmaceuticals Inc., [2]PharmacoMetrica

Background: The laboratory classroom study design is intended to evaluate the time course (onset and duration) of drug effects on ADHD symptoms throughout the day. Dasotraline is a novel dopamine and norepinephrine reuptake inhibitor which achieves stable plasma concentrations over 24 hours. Dasotraline treatment was evaluated in children with ADHD in a randomized, double-blind laboratory classroom study (NCT02734693). However, in contrast to prior classroom studies, a classroom day was conducted prior to randomization as a pre-treatment baseline (Day 1). The effects of treatment were analyzed at endpoint (Day 15) following 14 days of treatment with placebo or dasotraline (4 or 6 mg/day). The objective of this analysis was to develop an exposure-response model of dasotraline effects on ADHD symptoms throughout the day using the Swanson, Kotkin, Agler, M-Flynn, and Pelham scale (SKAMP).

Methods: The study enrolled children ages 6-12 years who met DSM-5 criteria for a primary diagnosis of ADHD with an ADHD Rating Scale Version IV total score ≥26. The trajectory of SKAMP scores throughout the day was modeled using an indirect response model with a time-varying effect in patients treated with placebo (N=56) and dasotraline (N=56). The exposure to dasotraline was analyzed by individual subject's weight-adjusted doses (mg/kg) and individual subject's plasma concentrations, as predicted by a previously-developed population PK model (plasma drug concentrations were not collected in this study).

Results: The indirect-response longitudinal model provided a reasonable characterization of the exposure-response relationship of dasotraline, together with an accurate description of the trajectories of SKAMP-Combined scores, and SKAMP-Attention and SKAMP-Deportment subscale scores throughout the day. Notably, exposure to dasotraline had a dual effect on SKAMP scores: a marked reduction in the onset of ADHD symptoms in the classroom (SKAMP-Deportment), combined with an overall reduction in the intensity of ADHD symptoms throughout the day (SKAMP-Attention), resulting in almost flat SKAMP trajectories (SKAMP-Combined Scores) throughout the 12-hour classroom assessment time-period.

Conclusions: The exposure-response dasotraline model provided a good description of the effect of dasotraline on the trajectory of SKAMP scores in patients throughout the classroom day. These results provide a quantitative description of how stable dasotraline exposures provide sustained improvement in ADHD symptom severity, and quantify the dual effects of dasotraline on ADHD symptoms of inattention and hyperactivity over the course of the day.

63. COMPARATIVE BIOAVAILABILITY OF DR/ER-MPH, A DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE FORMULATION, AND AN IMMEDIATE-RELEASE METHYLPHENIDATE IN HEALTHY ADULT VOLUNTEERS

Bev Incledon*[1], Norberto DeSousa[1], F. Randy Sallee[1]

[1]Ironshore Pharmaceuticals & Development Inc.

Background: Evening-dosed DR/ER-MPH (formerly HLD200) is a delayed-release and extended-release methylphenidate (MPH) formulation designed to delay initial drug release and provide an onset of treatment effect upon awakening and lasting into the evening. This study compared the relative bioavailability of MPH after a single dose of DR/ER-MPH to that of an immediate-release MPH (IR MPH) administered in the morning.

Methods: This was a phase 1, single-center, single-dose, open-label, randomized, 2-way crossover, pharmacokinetic (PK) study of healthy adult volunteers randomized to DR/ER-MPH (100 mg) or IR MPH (20 mg). Blood samples were analyzed for plasma MPH (DR/ER-MPH: predose–48 h; IR MPH: predose–24 h). The following PK parameters were evaluated: maximum plasma concentration (Cmax), time to Cmax (Tmax), area under the curve from time zero to last quantifiable concentration (AUC), and apparent terminal half-life (t1/2). Comparable bioavailability was concluded if the 90% confidence intervals (CI) for the ratios between DR/ER-MPH and IR MPH for dose-normalized [DN] ln-transformed AUC and Cmax were within 80%–125%. Safety measures, including adverse events (AEs), laboratory tests, vital signs, and electrocardiograms (ECGs), were also assessed.
Results: Twelve participants were randomized to 2 treatment sequence cohorts (n = 6). Median Tmax (range) was 14.0 h (10.5–15.0 h) following a single evening dose of DR/ER-MPH and 1.5 h (1.0–2.0 h) after morning administration of IR MPH. While mean Cmax and AUC were higher for DR/ER-MPH (10.46 ng/mL and 120 h·ng/mL) versus IR MPH (7.05 ng/mL and 32.3 h·ng/mL), DN Cmax and AUC values were lower in DR/ER-MPH (0.105 [ng/mL]/mg and 1.20 [h·ng/mL]/mg) versus IR MPH (0.352 [ng/mL]/mg and 1.62 [h·ng/mL]/mg). Mean t1/2 was ~2.2 hours longer with DR/ER-MPH versus IR MPH (6.02 vs. 3.79 h). Total exposure was significantly different between DR/ER-MPH and IR MPH (DN AUC: P=0.0052; DN Cmax: P<0.0001) and 90% CI were outside the limits for comparable bioavailability. After a single dose, the estimated MPH bioavailability of DR/ER-MPH relative to IR MPH was 73.9% based on DN AUC. Following a single dose, no serious or severe AEs were reported in either treatment group and AEs were consistent with MPH. Furthermore, no sleep-related or appetite-related AEs were reported. No safety effects were observed related to clinical laboratory, vital signs, or ECG results.
Conclusions: Evening-dosed DR/ER-MPH demonstrated a consistent delay in initial drug release, followed by subsequent controlled drug release throughout the day. The relative bioavailability of a single dose of DR/ER-MPH to a single dose of IR MPH was 73.9%. Consistent with the formulation differences, DR/ER-MPH exhibited a longer Tmax and t1/2 versus IR MPH. The safety profile of DR/ER-MPH and IR MPH was consistent with the established safety profile of MPH.

**64. ATTENTION DEFICIT/HYPERACTIVITY DISORDER, SCHOOL ACHIEVEMENT AND THE EFFECT OF MEDICATION: EVIDENCE FROM A SWEDISH PRIMARY SCHOOL POPULATION

Andreas Jangmo*[1], Amanda Stålhandske[1], Ralf Kuja-Halkola[1], Henrik Larsson[2]

[1]Karolinska Institute, [2]Karolinska Institute & Örebro University

Background: Individuals with ADHD are at increased risk of school underachievement and treatment with ADHD medications may have beneficial effects on school performance. Previous research has shown that ADHD medication can provide benefits in terms of school achievement, but follow-up times have usually been short, sample sizes small and/or limited to clinical settings.
Methods: Using Swedish national registers we evaluate whether pharmacological treatment of ADHD has an effect on grade points in standardized tests, leaving certificates, eligibility to, and completion of, upper secondary school in a student population of 657,720 individuals graduating from year 9 of compulsory school between 2008 and 2013.
Results: Our results confirmed previous research that ADHD is associated with substantially lower school achievement and that this relationship is not driven by parental socioeconomic background factors. Treatment with ADHD medication was associated with greater school

achievements where each additional 3-month treatment period was associated with an increase in the sum of grade points of 4.51 points, 95% CI= 4.13- 4.89 corresponding to an increase in the grade point average of 0.25 points, 95% CI=0.22-0.27. Increases in the probability of being eligible to, and completing, upper secondary school was also observed.
Conclusions: ADHD has a substantial negative impact on school achievement and pharmacological treatment for ADHD is associated with improvements in several of these outcomes. Our findings highlight the need to detect and treat ADHD at an early stage and that multimodal treatment efforts are probably needed to reduce the negative impact of ADHD on school achievement.

65. DOUBLE-BLIND SHAM-CONTROLLED PILOT STUDY OF TRIGEMINAL NERVE STIMULATIOIN (TNS) FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

James McGough*[1], Sandra Loo[1], Jennifer Cowen[1], Alexandra Sturm[1], Ian Cook[1]

[1]David Geffen School of Medicine at UCLA

Background: Trigeminal nerve stimulation (TNS), a minimal risk, non-invasive method of neuromodulation, has proven effective in treatment-refractory depression and epilepsy and is associated with increased activation in the anterior cingulate gyrus on PET imaging. A previous open-label investigation suggested potential benefits of TNS in treating ADHD, but was neither controlled nor conducted in blinded fashion. This double-blind, sham-controlled study is the first blinded controlled study of TNS in youth and first to examine the efficacy of TNS as an ADHD treatment.
Methods: Children aged 8-12 years, with minimal full scale IQ=85 and KSADS diagnosed ADHD, were randomized to 4 weeks nightly treatment with active or sham TNS. In the active group, low-grade electrical stimulation was generated during sleep by a small device worn on the participant's shirt and administered via an electrode patch applied to the forehead each night at bedtime. Active vs. sham treatments were identical except that no stimulation was administered with sham. Assessments included weekly clinical administered parent ADHD-rating scales (ADHD-RS) and CGI severity and improvement scales, and parent- and teacher-completed Conners' ratings. Cognitive testing and EEG were conducted at selected visits. Dimensional outcomes were fitted via a mixed effects model with group*time interaction to test for differential effects of active treatment using a piecewise linear time trend.
Results: Total N-62. ADHD-RS total scores showed significant group*time effects (F df1/df2 = 8.12 1/228, p=.05), with Cohen's d estimate at Visit 4 = .5, suggesting a medium-sized effect. CGI-I provident favored active treatment (Chisq = 9.12 df=1, p-.003). There were no significant differences in weight, height, pulse or blood pressure, or expectation of improvement. There were no clinically meaningful side effects or adverse events in either condition.
Conclusions: Although limited by a small-sized sample and short-term duration, this study demonstrated potential efficacy of TNS as an ADHD therapy, and provides further evidence that TNS is safe and of minimal risk in children. Ongoing analyses will examine potential TNS effects on cognition, brain activation and neural circuitry. Future research is needed to assess the durability of treatment response and impact on brain development with sustained use. (clinicaltrials.gov registration: NCT02155608).

66. ADAIR: AN ABUSE DETERRENT ORAL FORMULATION OF IMMEDIATE RELEASE DEXTRO-AMPHETAMINE SULFATE (D-AMPHETAMINE)

Jonathan Rubin*[1], David Siner[2], David Baker[2]

[1]Consultant, [2]Alcobra Pharma

Background: Amphetamine, a central nervous system stimulant, is commonly used for the treatment of Attention Deficit Hyperactivity Disorder. Immediate release (IR) stimulants are abused more frequently than extended release stimulants, and are frequently diverted. Furthermore, intranasal (IN) administration of stimulants is seen in 40% of college students who abuse stimulants.
In a study of stimulant abuse by adults admitted for abuse treatment, 38% used the IN route, and 10% injected stimulants by the intravenous (IV) route.

Intranasal abuse often involves the physical manipulation of a drug to reduce the product particle size. The Food and Drug Administration has determined that a clinically meaningful measure of deterrence is the percent mass of particles (<500 μm) available for insufflation.

To facilitate IV injection, the drug needs to be solubilized into a liquid that can be aspirated into a syringe. For a drug abuser, the attractiveness of the solubilized drug is largely influenced by its viscosity, affecting the force needed to push the plunger of the syringe through the needle and into the vein.

The current study sought to explore the physical properties, related to both IN and IV abuse deterrence characteristics, of an Abuse Deterrent Formulation of immediate release d-amphetamine (ADAIR), in comparison with the physical properties of IR d-amphetamine.

Methods: Resistance to physical manipulation of ADAIR, as compared with marketed IR d-amphetamine 10 mg tablet, was explored by milling with a coffee grinder, crushing with a mortar and pestle, and using a scalpel. The physically manipulated product was placed in a sieve array ranging from 0.106 mm to 1 mm, and the mass retained on each sieve was measured. Injectability assessments and texture analysis analyzed the relative potential for abuse via IV injection of ADAIR and d-amphetamine 10 mg tablet
Results: The physically manipulated preparation could not appreciably pass through a 500 μm sieve, a particle size deemed unsuitable for insufflation. In contrast, 42-47% of comparator passed through the 500 μm sieve, suggesting it could be insufflated. In comparison with IR d-amphetamine, ADAIR demonstrated reduced syringeability across a range of volumes of water (2, 5 and 10 ml), needle gauges (26, 23, 20 and 18 gauge), in ambient or hot water, and when passed through a cigarette filter. ADAIR mixed in water yielded a viscous, cloudy material, which was usually impossible, and at other times difficult, to syringe. Texture analysis demonstrated that the force required to push the plunger with an ADAIR filled syringe is far greater than that with manipulated IR d-amphetamine.
Conclusions: 1. Physical manipulation of ADAIR using either a coffee grinder, kitchen grater, scalpel, mortar and pestle, heating or cooling, resulted in a preparation that could not appreciably pass through a 500 μm sieve, a particle size deemed unsuitable for insufflation.
2. The syringeability study results demonstrate that the recovery of d-amphetamine was consistently lower in ADAIR compared to IR d-amphetamine.

3. The force required to push the plunger with an ADAIR filled syringe is far greater than that with manipulated IR d-amphetamine, suggesting that manipulated ADAIR is technically difficult/impractical to syringe, and may pose a danger if introduced intravenously.

4. Addressing IR stimulant abuse represents a major unmet need. If approved, ADAIR could present a deterrent to IN and IV abuse of IR d-amphetamine, a public health concern.

67. UNDERSTANDING ABUSE RISK RELATED TO IMMEDIATE-RELEASE AMPHETAMINE

Jonathan Rubin*[1], David Baker[2], David Siner[2], Natasha Oyedele[3]

[1]Consultant, [2]Alcobra Pharma, [3]Inflexxion

Background: While effective in the treatment of ADHD, CNS stimulants have been shown to have a high risk for abuse. Studies report that 40% or more of the people who misuse stimulants, particularly immediate release stimulants, do so by snorting or injecting them. In order to further explore the incidence, as well as demographics and nature of amphetamine abuse in the US, data was analyzed from the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) system. NAVIPPRO is a national program that includes surveillance of substance abuse as well as prevention and intervention educational programs for substance abuse.

Methods: The analysis examined the past 30-day abuse of immediate-release (IR) amphetamine prescription stimulant products (Adderall® (brand and generic), Dexedrine® and DextroStat®), in comparison to extended-release (ER) amphetamine prescription stimulant products (Adderall XR® (brand and generic), Vyvanse®, and Dexedrine Spanules®), as well as the past 30-day abuse of any amphetamine prescription stimulant product, including IR amphetamine and ER amphetamine. The analysis of the abuse of amphetamine products, categorized as IR amphetamine, ER amphetamine or all amphetamine, was conducted among a sentinel population of adult patients entering substance abuse treatment or assessed for substance abuse problems using the proprietary data stream from the NAVIPPRO system: the Addiction Severity Index-Multimedia Version (ASI-MV®). The Addiction Severity Index (ASI) is a structured clinical interview used to measure the severity of a range of problem areas typically associated with alcohol and drug abuse: Medical Status, Employment Status, Drug Use, Alcohol Use, Legal Status, Family and Social Relationships, and Psychiatric Status. The ASI- MV® is a self-report version of the ASI.

The study examined data in the ASI-MV® obtained from self-report of adult patients during the period from January 1, 2010 to September 30, 2016 (Q1 2010 –Q3 2016). Data obtained included the rate of past 30-day abuse, the route of abuse, the source of procurement of the amphetamine product, and the drug severity score. Abuse rates were calculated by two methods: the number of abuse cases per 100 ASI reports as well as the number of abuse cases per 100,000 prescriptions dispensed of the drug category.

Results: Among the 7,837 adult (18+ years) stimulant abusers assessed, past 30-day abuse of IR amphetamines (5.48 cases per 100,000 prescriptions), was greater than that for ER amphetamine products (2.93 cases per 100,000 prescriptions). Ingestion and/or chewing were the most commonly cited routes of abuse among the stimulant abusers, followed by insufflation and injection. The rate of abuse by insufflation was higher for IR amphetamines as compared with ER amphetamines. Among the subgroup of intravenous and intranasal amphetamine abusers, the rate of abuse for IR amphetamine products was double that of ER amphetamine products, and the overall drug problem severity was higher for abusers of IR amphetamine products. The most frequently reported source for amphetamine drug among abusers was

family/friend (57.1%), followed by dealer (25.9%), and abuse of the patient's own prescription (18.8%).
Conclusions: These analyses suggest that abuse of IR amphetamine products is common among prescription stimulant abusers, and the frequency of more dangerous ways of abuse (via the IV or intranasal routes) affirms the magnitude of the public health problem.

68. A RANDOMIZED, OPEN-LABEL BIOEQUIVALENCE STUDY OF A NEW EXTENDED-RELEASE AMPHETAMINE ORAL SUSPENSION IN ADULTS

Carolyn Sikes*[1], Jeffrey Stark[2], Russ McMahen[1], Dorothy Engelking[1]

[1]Neos Therapeutics, [2]Worldwide Clinical Trials

Background: Because individuals with ADHD display variability in responses to different therapies, lifestyle requirements, and degree of impairment, treatment should be individualized to achieve optimal outcomes. To this end, a new extended-release amphetamine oral suspension (AMP ER-OS) has been developed for the treatment of ADHD. AMP ER-OS is composed of delayed-release and immediate-release particles containing a 3:1 mixture of d- and l-amphetamine. The purpose of this study was to compare the rate of absorption and oral bioavailability of AMP ER-OS with a reference product (extended-release mixed amphetamine salts [MAS ER]).
Methods: This was a single-dose, open-label, randomized, 2-period, 2-treatment crossover study. Healthy adult volunteers received 15 mL of AMP ER-OS (equivalent to 30 mg of MAS ER) in 1 period, and a 30 mg MAS ER capsule in another period. Treatment periods were separated by 7 days and each was preceded by a 10-hour overnight fast. Randomization was performed using S-PLUS version 6.1. Blood samples were analyzed for d- and l-amphetamine concentrations at prespecified time points. Pharmacokinetic parameters for the peak plasma concentration (Cmax), area under the concentration-time curve from 0 to 5 hours (AUC0-5), area under the concentration-time curve from 5 hours to the last quantifiable concentration (AUC5-last), area under the concentration-time curve extrapolated to infinity (AUCinf), half-life (T1/2), and time to maximum plasma amphetamine concentration (Tmax) were calculated. The geometric mean ratio (AMP ER-OS/MAS ER; GMR) and the 90% confidence interval (CI) were calculated for log-transformed Cmax, AUC0-5, AUC5-last, and AUCinf for both d- and l-amphetamine. Bioequivalence was established if the 90% CIs fell within the 80% to 125% interval. Clinical evaluations were performed throughout the study to assess safety and tolerability.
Results: All 42 subjects completed both treatment periods. AMP ER-OS and MAS ER displayed comparable concentration-time profiles. For both treatments, Tmax of d- and l-amphetamine was a median of 5 hours, and T1/2 for each enantiomer was similar between treatments. The 90% CIs for the GMRs of Cmax, AUC0-5, AUC5-last, and AUCinf fell within the accepted 80% to 125% range for establishing bioequivalence for d- and l-amphetamine. Twelve adverse events were reported by 8 subjects and all were mild. The most common treatment-emergent adverse events were nausea (AMP ER-OS, n = 1 [2.4%]; MAS ER, n = 2 [4.8%]) and decreased appetite (AMP ER-OS, n = 2 [4.8%]; MAS ER, n = 1 [2.4%]).
Conclusions: AMP ER-OS is bioequivalent to MAS ER in healthy adult subjects under fasted conditions, and the safety profile is consistent with other extended-release amphetamine medications.

69. PHARMACOSCINTIGRAPHIC AND PHARMACOKINETIC ANALYSIS OF CTX-1301, A NOVEL TRI-MODAL ORAL FORMULATION FOR RELEASE OF DEXMETHYLPHENIDATE IN HEALTHY ADULTS

Raul Silva*[1], Matt Brams[1], Arthur Straughn[1], Shane Schaffer[1], Steven Abele[1], Howard Stevens[2], Neil Masson[3]

[1]Cingulate Therapeutics, [2]BDD Pharma, [3]Royal College of Psychiatrists

Background: CTx -1301 is a dexmethylphenidate (d-MPH) tri-modal tablet formulation comprised of an immediate release layer, a second delayed extended-release layer, and a third delayed immediate-release core designed to provide a fast onset, and ultimately therapeutically active levels of d-MPH lasting 13-16 hours. Finally, designing a preparation with a controlled descent of d-MPH was envisioned to minimize the rebound effect and maintain favorable tolerability. The primary focus of the presentation is to describe how the third delayed core performed in terms of where it is delivered in the gut, and how successfully the delivery mechanism achieved the controlled descent.

Methods: A randomized, three-arm, open-label crossover study was performed in 15 healthy volunteers (mean age = 25 years; wt. = 77kg) to establish the PK profile of a novel dexmethylphenidate (d-MPH) modified-release tablet (CTx-1301) using pharmacoscintigraphic methods. Each volunteer underwent three treatment arms receiving a bi-phasic extended-release d-MPH 10mg (Focalin XR) (Treatment A), and CTx-1301 12.5mg tablets (Treatment B contained a radiolabelled second d-MPH layer, and Treatment C contained a radiolabelled third d-MPH layer). Serial blood samples were taken over a 24-hour period after dosing and plasma concentrations of d-MPH were analyzed for all three groups to determine relevant pharmacokinetic parameters including initial and subsequent Cmax and Tmax, as well as AUC (0-8 hrs), AUC (8-24), and AUCinf. Scintigraphic methods were used to visualize timing and location of release of radiolabeled d-MPH layers from CTx-1301 tablets.

Results: The two CTx-1301 treatment arms demonstrated initial Tmax (0-4h) of 1.6 hrs and 1.9 hrs versus 2.3 hrs for Focalin XR and initial Cmax (0-4h) (4.9 and 5.3 vs 5.9ng.ml-1). The terminal half-life was extended by more than an hour in the CTX-1301 treatments (4.5 and 4.3 hours) versus Focalin XR (3.0 hours). Scintigraphic measurements determined mean time of release of the CTx-1301 second layer to be 4.7 hr., and the third layer (core) to be 10.3 hr. There was a statistically significant ($p<0.005$) difference between mean AUC(8-24h) between CTx-1301 B and C (29.2 & 31.6 hr· ng/ml) and Focalin XR (17.1 hr· ng/ml). Onset of release of the second CTx-1301 layer was visualized in the small intestine (N=8), caecum (N=3), and ascending colon (N=4), while onset of release of the third layer was visualized in the small intestine (N=1), caecum (N=2), ascending colon (N=4), transverse colon (N=7), and splenic flexure (N=1). No serious adverse events were reported following any treatment.

Conclusions: Mean initial Cmax and Tmax values were comparable between the three treatment arms. Second and third delayed-release layers of CTx-1301 were delivered as designed, maintaining blood levels of d-MPH longer than Focalin XR resulting in a slower descent of d-MPH. Future investigations will include classroom studies to link the pharmacokinetics and clinical efficacy of CTx-1301, including the rebound effect.

70. L-METHYLFOLATE SUPPLEMENTATION TO OROS-METHYLPHENIDATE PHARMACOTHERAPY IN ADHD: A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED CLINICAL TRIAL

Craig Surman*[1], Tolga Atilla Ceranoglu[1], Carrie Vaudreuil[1], Brittany Albright[1], Mai Uchida[1], Amy Yule[1], Andrea Spencer[1], Heidi Boland[1], Rebecca Grossman[1], Lauren Rhodewalt[1], Maura Fitzgerald[1], Joseph Biederman[1]

[1]Massachusetts General Hospital

Background: Interventions for Attention Deficit Hyperactivity Disorder (ADHD) may be inadequate for some patients. There is evidence that supplementation with L-methylfolate augments antidepressant agent effects, and thus might also augment ADHD treatment effects by a common catecholaminergic mechanism.
Methods: 44 adults with DSM-5 ADHD participated in a randomized, double-blind, placebo controlled, 12-week trial of 15 mg of L-methylfolate in combination with OROS-methylphenidate. OROS-methylphenidate was dosed-optimized over the first six weeks. We evaluated effects on ADHD symptoms, self-report on the Behavior Rating Inventory of Executive Function (BRIEF) of executive function, methylphenidate dosing, neuropsychological test measures, the Adult Self Report (ASR) scale, emotional dysregulation, social adjustment and work productivity, as well as moderating effects of body mass index, autoantibodies to folate receptors, and select genetic polymorphisms.
Results: L-methylfolate was well tolerated, with no significant effect over placebo except improvement from abnormal measures on the Mean Adaptive dimension of the ASR scale ($\chi 2=4.36$, $p=0.04$). Methylphenidate dosing was significantly higher in individuals on L-methylfolate over time ($\chi 2=7.35$, $p=0.007$). Exploratory analyses suggested variation in a GTP cyclohydrolase gene predicted association with higher doses of methylphenidate ($p <0.001$).
Conclusions: L-methyfolate was associated with no change in efficacy on measures relevant to neuropsychiatric function in adults with ADHD, other than suggestion of reduced efficacy of methylphenidate. Further investigation would be required to confirm this effect and its mechanism, and of genotype prediction of effects on dosing and executive function.

71. POPULATION PHARMACOKINETIC-PHARMACODYNAMIC MODELING OF A NOVEL METHYLPHENIDATE EXTENDED-RELEASE ORALLY DISINTEGRATING TABLET IN PEDIATRIC PATIENTS WITH ADHD

Nathan Teuscher*[1], Carolyn Sikes[2], Russ McMahen[2], Dorothy Engelking[2]

[1]Certara, [2]Neos Therapeutics

Background: Effective attention-deficit/hyperactivity disorder (ADHD) treatment requires a variety of stimulant formulations to fulfill guideline-recommended treatment individualization. While oral disintegrating tablets (ODTs) have demonstrated benefits in many disease areas, they are not available for methylphenidate (MPH) in ADHD treatment. A novel MPH extended-release ODT (MPH XR-ODT) has recently been approved, and this analysis sought to determine the correlation between plasma drug concentrations and key efficacy measures using a modeling-based approach. A population pharmacokinetic (PK)-pharmacodynamic (PD) model was developed to describe the PD-response data in an ADHD pediatric classroom study of MPH XR-ODT and to simulate the PD responses for pediatric patients across a range of body weights and MPH XR-ODT doses.
Methods: The PK-PD model was based on data from a phase 3, randomized, controlled laboratory classroom study in pediatric patients with ADHD and a previously established pediatric PK model. The classroom study evaluated the efficacy of MPH XR-ODT using the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP) Combined score. The PK model was a 2-input, 1 compartment, first order elimination model with body weight as a covariate on clearance and volume of distribution. The model was used to simulate maximum

reduction in the SKAMP Combined scores and SKAMP Combined scores across a range of body weights (7–100 kg) and dose levels (equivalent to 10–60 mg MPH HCl).
Results: The maximal reduction in SKAMP combined score was approximately 38 units, and the MPH concentration required to achieve 50% of the maximal reduction was 14.24 ng/mL, suggesting favorable efficacy for MPH XR-ODT. Model simulation suggested that patients with higher body weights required larger doses of MPH XR-ODT for symptom control. For patients with body weights ranging from 26 pounds to 218 pounds, the optimal MPH XR-ODT doses were 10 mg to 60 mg in terms of MPH HCl. A favorable safety profile for MPH XR-ODT may be anticipated because of the lack of discontinuations due to adverse events in either study.
Conclusions: There was a direct correlation between the dose of MPH XR-ODT required for symptom control and patient body weight. Given that data on the PK-PD relationship for ADHD medications are limited, using the PK-PD model to predict the optimized dose for individual pediatric patients can minimize the lengthy dose-titration process and provide insight into a target dose.

72. EFFICACY AND SAFETY OF DASOTRALINE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A LABORATORY CLASSROOM STUDY

Sharon Wigal[1], Seth Hopkins[2], Kenneth Koblan[2], Ann Childress[3], Joyce Tsai[2], Jay Hsu[2], Antony Loebel[2], Robert Goldman*[2]

[1]AVIDA Inc., Newport Beach, CA, [2]Sunovion Pharmaceuticals Inc., [3]Center for Psychiatry and Behavioral Medicine, Inc., Las Vegas, Nevada,

Background: Dasotraline is a potent inhibitor of pre-synaptic dopamine and norepinephrine with a profile characterized by slow absorption, a long elimination half-life, and low abuse potential. We report here the results of a laboratory classroom study whose aim was to evaluate the efficacy and safety of dasotraline for the treatment of ADHD in children.
Methods: Children (ages 6-12; N=112; male, 69%) with a diagnosis of attention-deficit hyperactivity disorder (ADHD), treated with stable doses of methylphenidate, and who completed a 3-5-day washout, were randomized, double-blind, to a 14-day course of parallel-group treatment with dasotraline 4 mg/d (evening dosing) or placebo. Efficacy was measured in a laboratory classroom setting at Baseline (prior to treatment) and at Day 15 (after 14-days of treatment) using the Swanson, Kotkin, Agler, M-Flynn, and Pelham scale (SKAMP-combined score, the primary endpoint), and the Permanent Product Measure of Performance (PERMP) math test. In seven 30-minute laboratory classroom sessions (from 8AM to 8PM; 12-24 hours post-dose) on each study day, trained observers used the SKAMP and PERMP to assess the presence and severity of behavioral and attentional manifestations of ADHD.
Results: Fourteen days of treatment with dasotraline 4 mg/d was associated with significant improvement from baseline in the SKAMP-combined score (-3.2 vs. +2.0; $P<0.001$; effect size, 0.85), the SKAMP-attention subscale score (-0.7 vs. +0.8; $P<0.001$; effect size, 0.81) and the SKAMP-deportment subscale score (-1.4 vs. +0.2; $P<0.001$; effect size, 0.70). Significant improvement in ADHD symptoms was maintained through the final (8PM) assessment time-point (up to 24 hours post-dose). The 3 most common adverse events for dasotraline (vs. placebo) were insomnia (19.6% vs. 3.6%), headache (10.7% vs. 8.9%) and decreased appetite (10.7% vs. 3.6%).
Conclusions: In this placebo-controlled laboratory classroom study, dasotraline, taken as a 4 mg evening dose, was found to be a safe and efficacious treatment of ADHD in children ages

6-12 years. The results found that dasotraline provided steady-state, 24-hour coverage of the symptoms and behaviors of ADHD with once-daily dosing

Clinicaltrials.gov: NCT02734693

Sponsored by Sunovion Pharmaceuticals, Inc.

73. DASOTRALINE FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN ADULTS: POOLED ANALYSIS OF TWO DOUBLE-BLIND STUDIES

Lenard Adler[1], Scott Kollins[2], Seth Hopkins[3], Robert Goldman[3], Joyce Tsai[3], Jay Hsu[3], Andrei Pikalov[3], Kenneth Koblan[3], Antony Loebel[3], Andrei Pikalov*[3]

[1]New York University Langone Medical Center, [2]Duke University Medical Center, [3]Sunovion Pharmaceuticals Inc.

Background: Dasotraline is a potent inhibitor of pre-synaptic dopamine and norepinephrine with a profile characterized by slow absorption, a long elimination half-life, and low abuse potential. The aim of this pooled post-hoc analysis was to evaluate the efficacy and safety of dasotraline in once-daily doses ranging from 4-8 mg in adults with ADHD.
Methods: Data were pooled from two randomized, double-blind, placebo-controlled studies of fixed-doses of dasotraline for the treatment of adults with ADHD. Study 1 was a 4-week study utilizing dasotraline in fixed doses of 4 mg/d (N=116) and 8 mg/d (N=115) vs. placebo (N=110). Study 2 was an 8-week study utilizing dasotraline in fixed doses of 4 mg/d (N=210) and 6 mg/d (N=207) vs. placebo (N=219). The current pooled analysis included efficacy data from the first 4 weeks of Study 2 (the common endpoint in both studies), and safety data from the full 8 weeks. Efficacy assessments included the ADHD Rating Scale (ADHD RS-IV), and the Clinical Global Impression, Severity (CGI-S) scale, modified for ADHD symptoms, and were analyzed using a mixed model for repeated measures (MMRM) analysis.
Results: The pooled safety sample consisted of 973 patients (mean age 34 years, 53% male; mean ADHD RS-IV score, 38.5). Treatment with dasotraline was associated with statistically significant Week 4 improvement in the ADHD RS-IV total score for the 4 mg/d dose ($P<0.05$), 6 mg/d dose ($P<0.05$), and 8 mg/d dose ($P<0.01$). Treatment with dasotraline was associated with statistically significant Week 4 improvement in the CGI-Severity score for the 4 mg/d dose (-1.1; P=0.015), 6 mg/d dose (-1.1; P=0.031), and 8 mg/d dose (-1.3; P=0.003). Discontinuation rates for the pooled sample were as follows (based on the full duration of each study): dasotraline 4 mg/d (30.1%), 6 mg/d (38.6%), 8 mg/d (50.4%), and placebo (19.5%). The most frequent adverse events associated with dasotraline were insomnia, decreased appetite, and dry mouth. The majority of adverse events were mild-to-moderate in severity. There were no clinically meaningful changes blood pressure or heart rate on dasotraline.
Conclusions: This pooled post-hoc analysis found dasotraline (4-8 mg/d) to be a safe and efficacious treatment for ADHD in adults that provided steady-state, 24-hour coverage with once-daily dosing.

Sponsored by Sunovion Pharmaceuticals, Inc.

74. EFFICACY, SAFETY, TOLERABILITY AND PK OF MAZINDOL CONTROLLED RELEASE (CR) IN ADULTS WITH ADHD

Tim Wigal*[1], Jeffrey Newcorn[2], Sharon Wigal[1], Nelson Handal[3], Iouletta Mulligan[4], Virginia Schmith[5], Eric Konofal[6]

[1] AVIDA Inc., [2]Mount Sinai Medical Center, [3]Dothan Behavioral Medicine Clinic, [4]Worldwide Clinical Trials, [5]Nuventra Pharma Sciences, [6]Pediatric Sleep Disorders Center

Background: Mazindol was originally developed as an appetite suppressant in 1973, but was withdrawn from US/European markets by 2002 for commercial reasons (unrelated to efficacy or safety). Mazindol CR is a new formulation with a lower Cmax than the IR tablet and an equivalent AUC. The primary objective of this study was to evaluate the efficacy of Mazindol CR in adult patients with ADHD. Additionally, the safety, tolerability and PK were assessed.
Methods: This was a randomized, double-blind, placebo-controlled, flexible dose trial of Mazindol CR vs. placebo (1:1) for 6 weeks in 85 participants with ADHD. The Mazindol CR dose was titrated (1 mg QD x 7 days, then 2 mg QD x 7 days, then 3 mg QD x 7 days) based on clinical response and tolerability. Dose reductions in the final 4 weeks of the study were allowed due to lack of tolerability. The primary endpoint was the reduction from baseline in ADHD--DSM5 clinician-rated scale score at the end of treatment (Day 42). Secondary endpoints were responders as measured by a 30% and a 50% reduction in rating scores and by Clinical Global Impressions Improvement (CGI-I) at end of treatment. Safety and tolerability were assessed through adverse event reporting (AEs), vital signs, physical examination, laboratory parameters, and assessment of suicide risk at each weekly visit.
Results: Using a repeated-measures mixed-effect model, mazindol was different from placebo for each weekly measurement beginning at Day 7 ($p<0.005$), with a LS Mean difference (Mazindol CR-Placebo) of -13.2 ($p<0.001$) at Day 42 (ITT population) with an effect size of 1.09. There were significantly more responders for Mazindol CR compared to placebo ($p<0.001$) as defined by both a 30% and a 50% reduction ADHD-RS-DSM5 rating scale scores and by CGI-I (1 or 2). AEs were reported in 31 and 21 participants from the Mazindol CR and placebo group, respectively. The primary AEs were dry mouth (23% vs 4.8%), heart rate increased/tachycardia (16% vs 0%), decreased appetite (9.3 vs 7.1%) and heart rate increased/tachycardia (16% vs 0%). Overall, mazindol CR had a moderate effect on heart rate and a small effect on blood pressure. No serious AEs were reported and only the only participant discontinued due to an AE was in the placebo group.
Conclusions: This study demonstrated that Mazindol CR was efficacious in the treatment of adults with ADHD, with a large effect size of 1.09, and was well-tolerated, supporting the progression to Phase 3 studies.

**75. THE ASSOCIATION BETWEEN ADHD MEDICATION AND SEIZURES

Kelsey Wiggs*[1], Zheng Chang[2], Patrick Quinn[1], Kwan Hur[3], Robert Gibbons[3], David Dunn[4], Isabell Brikell[2], Henrik Larsson[5], Brian D'Onofrio[1]

[1]Indiana University, [2]Karolinska Institute, [3]University of Chicago, [4]Indiana University School of Medicine, [5]Karolinska Institute & Örebro University

Background: Individuals with ADHD are at increased risk of seizures, but there is uncertainty about whether ADHD medication treatment increases risk among patients with and without pre-existing seizures. The aim of the current study was to examine the association between ADHD medication and seizures among ADHD patients in a large commercial health insurance claims database. To accomplish this aim, we used a research design that compares the risk of seizures when an individual received ADHD medication with when the same individual did not to adjust for all stable confounding factors; measured covariates adjusted for time-varying factors.

Methods: We followed a sample of 801,838 ADHD patients with prescribed drug claims from the Truven Health MarketScan® Commercial Claims and Encounters databases between the years 2005 and 2013. We identified seizure events with insurance claims for emergency room visits, ambulance rides, and inpatient hospitalizations. We established previous seizure history by any seizure claim in the year prior to the index date. We ran a series of analyses to explore seizure risk associated with ADHD and ADHD medication. First, we assessed overall risk of seizures among ADHD patients. Second, within-individual concurrent analyses assessed odds of seizure events during months when ADHD patients were prescribed ADHD medication compared with when they were not, while adjusting for filled prescriptions of antiepileptic medications. Third, within-individual long-term analyses examined odds of seizure events associated with the number of months dispensed the medication during the previous two years while adjusting for concurrent antiepileptic and ADHD medication. Fourth, we conducted several within-individual sensitivity analyses to test for bias in findings as a result of analytic decisions.
Results: ADHD patients were at higher odds for at least one seizure compared with non-ADHD controls (OR=2.33, CI=2.24-2.42 males; OR=2.31, CI=2.22-2.42 females). In adjusted within-individual comparisons, ADHD medication was associated with lower odds of seizure events among patients with (OR=0.71, CI=0.60-0.85) and without (OR=0.71 CI=0.62-0.82) prior seizures. Thus, patients were less likely to have a seizure during a month they were dispensed ADHD medication than months when the same individual was not. Long-term within-individual estimates also suggested no evidence of increased risk of seizure events associated with medication use among individuals that had a previous seizure history (OR=0.87 CI=0.59-1.30) and without (OR=1.01 CI=0.80-1.28). Finally, a series of sensitivity analyses provided converging evidence for our main findings. Specifically, changing our exposure and outcome definitions, restricting our sample to those that took no other psychotropic medications, and stratifying our analyses by sex and age did not change the main concurrent and long-term findings.
Conclusions: The results suggest that ADHD patients are at higher risk of seizures. However, ADHD medication was associated with lower risk of seizures within individuals while they were dispensed medication compared to when the same individuals were not. We found commensurate results when exploring the associations in patients with and without a prior seizure history. We also found no evidence of increased risk of seizures due to long-term ADHD medication use. These findings are not consistent with the hypothesis that ADHD medication increases risk for seizures.

76. CLINICALLY MEANINGFUL IMPROVEMENTS WITH DR/ER-MPH IN AT-HOME FUNCTIONAL IMPAIRMENT DURING THE EARLY MORNING, LATE AFTERNOON, AND EVENING IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Timothy Wilens*[1], Stephen V. Faraone[2], Paul Hammerness[3], Steven Pliszka[4], Norberto DeSousa[5], F. Randy Sallee[5], Bev Incledon[5], Jeffrey Newcorn[6]

[1]Massachusetts General Hospital, [2]SUNY Upstate Medical University, [3]Harvard Medical School, [4]UT Health Science Center at San Antonio, [5]Ironshore Pharmaceuticals & Development, Inc., [6]Mount Sinai Medical Center

Background: The efficacy and safety of DR/ER-MPH, a delayed-release and extended-release methylphenidate (formerly HLD200), were evaluated in a phase 3 trial of children with attention-deficit/hyperactivity disorder (ADHD). In addition to improving ADHD symptoms,

DR/ER-MPH demonstrated statistically significant reductions versus placebo in early morning and late afternoon/evening at-home functional impairment; however, it is unknown whether these improvements in at-home functional impairment are clinically relevant. This post hoc analysis evaluated the clinical meaningfulness of DR/ER-MPH versus placebo in improving at-home functional impairment.

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). At-home early morning functional impairment was assessed by the 20-item Before School Functioning Questionnaire (BSFQ) and the 3-item Parent Rating of Evening and Morning Behavior-Revised (PREMB-R) morning (AM) subscale. At-home late afternoon/evening functional impairment was assessed by the 8-item PREMB-R PM subscale. For BSFQ and PREMB-R subscales, items are rated from 0 to 3, with a higher score indicating greater severity. Clinically meaningful improvements in functional impairment were defined using anchor-based estimates with Clinical Global Impression-Improvement (CGI-I) scores of 1 (very much improved) and ≤2 (very much improved or much improved) as anchors. Cumulative percentages of children with changes from baseline in BSFQ, PREMB-R AM, and PREMB-R PM anchored to CGI-I were assessed. Chi-square tests were used to determine whether there were clinically meaningful differences between DR/ER-MPH and placebo.

Results: Reductions from baseline of 20 points on the BSFQ, 3 points on the PREMB-R AM, and 5 points on the PREMB-R PM were defined as clinically meaningful using CGI-I ≤2 as an anchor. Using these responder definitions, a significantly higher proportion of children receiving 3 weeks of DR/ER-MPH treatment versus placebo achieved clinically meaningful improvements from baseline in BSFQ (65.4% vs 43.3%; P=0.012), PREMB-R AM (73.4% vs 41.3%; P<0.001), and PREMB-R PM (64.6% vs 42.7%; P=0.01). When CGI-I of 1 was used as an anchor, reductions of 27 points on the BSFQ, 5 points on the PREMB-R AM, and 9 points on the PREMB-R PM were defined as clinically meaningful. Using these more stringent responder definitions, a significantly higher proportion of children treated with DR/ER-MPH versus placebo achieved clinically meaningful improvements from baseline in BSFQ (51.3% vs 23.9%; P=0.001), PREMB-R AM (45.6% vs 24.0%; P=0.008), and PREMB-R PM (46.8% vs 24.0%; P=0.005). No serious treatment-emergent adverse events (TEAEs) were reported and TEAEs were consistent with methylphenidate.

Conclusions: This post hoc analysis demonstrates that the previously reported statistically significant improvements in at-home functional impairment from the early morning until evening (as assessed by the BSFQ, PREMB-R AM, and PREMB-R PM) following 3 weeks of treatment with DR/ER-MPH are clinically meaningful.