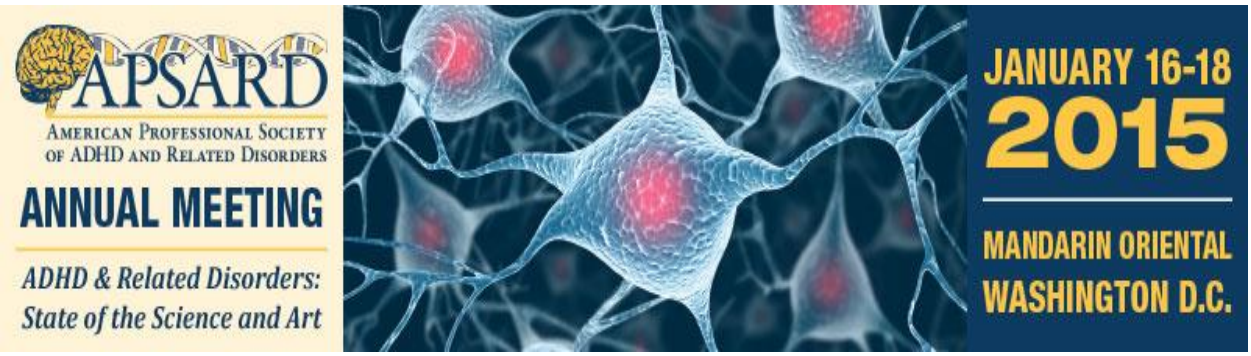

POSTER ABSTRACTS

1. ***Pharmacokinetic and Pharmacodynamic Properties of Lisdexamfetamine in Adults with ADHD***

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BACKGROUND: Lisdexamfetamine (LDX) is a pro-drug (d-amphetamine (d-amph) bound to lysine). Clinically, d-amph is available post-cleavage of the pro-drug in the blood stream. Clinical effects of LDX in ADHD have been shown to persist up to 14 hours; however pharmacokinetic (PK) data of LDX and Amph in ADHD adults is not currently available.
OBJECTIVES: 1) to examine PK data of plasma Amph and LDX levels and 2) to compare PK data with Time Sensitive ADHD Rating Scale (TASS) ratings (PK v. PD).
METHODS: Plasma Amph/LDX levels and TASS ratings were obtained immediately prior to AM dose and then 0.5, 1, 2, 4, 6, 8, 10 and 12 hours post-dosing in 21 adults with ADHD treated with five weeks of single-blind LDX up to 70 mg/day (after 1 week single-blind PBO).
RESULTS: LDX levels peaked at 1.5 hours after administration (T max) and then rapidly declined (levels were negligible at 6 hours), (area under the curve (AUC) = 45.9, Cmax = 25.0, and half-life (t½) = 0.5 hours). Amph levels peaked at (T max) 4.4 hours, but then slowly declined (AUC = 641.6, Cmax = 67.9, and t ½ = 17.0 hours). No significant correlations were seen between d-amph levels and TASS scores.
CONCLUSIONS: 1) pro-drug LDX levels peaked fairly rapidly and declined, while Amph levels peaked 3 hours later than LDX levels and persisted throughout the day and 2) the absence of PK/PD correlations may be due to subjects remaining in a controlled, non-attention demanding environment, potentially distorting TASS ratings.

3. ***Examination of Transgenerational Transmission of ADHD through the WHO ASRS v1.1 Screener***

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OBJECTIVES: To examine: 1) transgenerational transmission of ADHD via the ASRS v1.1 Screener in parents of children with ADHD, 2) potential contributions of socioeconomic status (SES)and executive function (EF) to the screen positive cohort.
METHODS: Parents of children diagnosed with ADHD at the NYU School of Child Study Center (CSC) were identified via record search of the electronic database. Subjects who agreed to participate received a survey via the telephone which included: 1) the 6-question ASRS Screener v1.1, 2) a supplemental 6 questions exploring EF, and 3) demographical questions including the Hollingshead SES Questionnaire.
RESULTS: The screen positive rate of parents of children with ADHD was 19.1%. There were no statistically significant differences in age, gender, race or SES between the screen positive and screen negative groups. The ASRS v.1.1 screen positive group had significantly higher average total EF score and a significantly greater number of EF symptoms at "significant level" (>= 3 "often"). A post-hoc factor analysis revealed three factors: Inattention (IA), Hyperactivity-Impulsivity (HI) and EF.
CONCLUSIONS: 1) The screen positive rate on the ASRS v1.1 Screener was higher than that found in the general population, but somewhat less than the expected rate, given reported

prevalence rates of 30%-40% in parents of children with ADHD. 2) A factor analysis revealed three factors of IA, HI and EF, similar to the findings of a large community based survey of ADHD symptoms (Kessler RC et al. 2010). 3) The screen positive cohort scored higher on questions of executive function.

4. ***Hypoconnectivity in Default Network Subsystems on Resting fMRI is Correlated with ADHD Hyperactive-Impulsive Symptoms***

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The default network, which is implicated in the representation of thoughts and cognition about oneself, is defined by increased BOLD activity during rest compared to when performing a task. A subcomponent of the default network, the dorsal medial prefrontal cortex (dMPFC) has been related to thinking about oneself in the present, while another subcomponent, the medial temporal lobe system (MTL) has been related to thinking about oneself in the future. Based on observations that individuals with ADHD tent to ignore the future consequences of their actions, leading to poor decision-making, we examined differences in intrinsic functional connectivity between these two default network systems in relation to a variety of ADHD symptom domains, as assessed by clinical rating scales, in a sample of 61 adults with ADHD and 75 controls. Significant positive correlations were found between the differences in default network BOLD activations between these two subsystems and subjects' standardized scores on subscales measuring hyperactivity, impulsivity and ADHD Total Symptoms of the Conners' Adult ADHD Rating Scale (CAARS), but only among those subjects who had T-score $\geq$ 65 on the CAARS DSM-IV Inattentive Symptoms Subscale. These results provide evidence of a dimensional relationship between severity of hyperactive and impulsive symptoms among these adults, with the degree of default network hypoconnectivity between its "now" and "future" subsystems. This suggests a potential brain-behavior relationship between dMPFC and MTL subsystem hypoconnectivity among more hyperactive and impulsive individuals which could underlie poor decision making observed among many individuals with ADHD.

5. ***Neural Mechanisms Underlying the Therapeutic Actions of Guanfacine Treatment in Youth with ADHD: A Pilot fMRI Study***

Anne Claude-Bedard[1], Kurt Schulz[1], Beth Krone[1], Juan Pedraza[1], Stephanie Duhoux[1], Jeffrey Halperin[1,2], Jeffrey Newcorn[1]
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Twenty-five youth with attention-deficit/hyperactivity disorder (ADHD) were scanned with functional magnetic resonance imaging while performing a go/no-go task before and after six to eight weeks of randomized once-daily treatment with either the α2A adrenergic receptor agonist guanfacine or placebo. Clinical improvement was greater for guanfacine than placebo and was differentially associated with reduced activation for guanfacine compared to placebo in right midcingulate cortex/supplementary motor area and left posterior cingulate cortex. Findings point to both common and unique mechanisms of action in relation to other stimulant and non-stimulant medications for ADHD.

6. ***Metadoxine Affects Brain Activity in Neural Circuits Associated with Cognitive Dysfunctions: A Pharmacological MRI Study in Conscious Rats***

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[1]Alcobra Ltd, [2]Center for Translational NeuroImaging, Northeastern University, [3]Ekam Imaging

Metadoxine Extended Release (MDX) previously showed cognitive improvement in clinical trials in adults with ADHD. To further elucidate brain activity of metadoxine, brain responses to metadoxine and its components, Pyridoxine and L-Pyroglutamic acid (L-PGA), were investigated using pharmacological magnetic resonance imaging (phMRI), based on blood oxygen level-dependent (BOLD) contrast.

When fully conscious, rats were administered a single intraperitoneal injection of vehicle, 75 or 150 mg/kg metadoxine, pyridoxine or L-PGA (75 mg/kg) and subjected to phMRI. Images were acquired every 6 seconds for 60-minutes and registered to a 3D rat brain atlas for analysis.

Metadoxine exhibited widespread negative BOLD activity in 28 brain regions and significant increased positive BOLD in only 7 of the 170 regions evaluated. The main areas displaying significant increased negative BOLD include the prefrontal cortex (PFC) (including prelimbic, 2nd motor, medial orbital, anterior cingulate), thalamus, caudate putamen, subregions of the cerebellum and primary somatosensory areas, regions associated with executive function, motivation, information processing and cognition.

None of the mesolimbic dopamine system areas involved in reinforcing effects of scheduled drugs were affected by metadoxine.

Metadoxine displayed a distinct phMRI fingerprint compared with approved ADHD therapies, the main difference being fewer areas exhibiting positive BOLD and a lack of effect on abuse-related areas. Metadoxine fingerprint was additionally distinct from its components.

Metadoxine's potential inhibitory effect on neuronal hyperactivity in cortical, striatal and verebellar regions could explain its precognitive activity. These findings extend previous data demonstrating a novel monamine-independent mechanism of action of metadoxine characterized by GABAergic inhibitory transmission modulation.

Two sentence summary: Pharmacologic magnetic resonance imaging of conscious rat using brain oxygen level dependent contrast demonstrated a fingerprint of reduced neuronal activity by metadoxine distinct from other ADHD medications. This fingerprint was characterized by reduced activity in areas thought to be hyperactivated in ADHD, as well as an absence of activity in areas of the brain associated with abuse.

7. ***Metadoxine - A Novel Synaptic Transmission Modulator with Low Abuse Potential in Development for Attention Deficit Hyperactivity Disorder (ADHD)***

Johanna Schumann[1], Jonathan Rubin[1], Yaron Daniely[1], Sharon L. Smith[2], Helen L. Rowley[2], David J. Heal[2], Amyaouch Bradaia[3], Bruno Buisson[3]
[1]Alcobra Ltd, [2]RenaSci Ltd, [3]Neuroservice

OBJECTIVE: Metadoxine Extended Release (MDX) has shown positiove results in clinical trials in adults with ADHD. To elucidate its mechanism of action, we have investigated (a) the neurochemical effect of metadoxine by microdialysis in rats (b) the electrophysiological effect on striatal medium spiny neurons and (c) its potential reinforcing effect in a self-administration model.

METHODS: Norepinephrine (NP), dopamine (DA) and serotonin (5 HT) levels were measured by microdialysis in rat prefrontal cortex (PFT) and striatum (STR) after a single oral dose of metadoxine (150 or 300 mg/kg). Passive membrane properties and miniature inhibitory post-synaptic currents (miPSC) were recorded from mice cortostritial slices treated with metadoxine (100, 200 or 300 μM) using whole-cell patch clamp. Self-administration was conducted in rates, first trained with methylphenidate (0.1 mg/kg, iv) on a fixed ration 2 schedule of reinforcement and then tested with metadoxine (0.3, 1.0, 3.0 or 10 mg/kg, iv).
RESULTS: Microdialysis did not reveal any effect of methadoxine on extracellular levels of DA, NE or 5-HT in PFC or STR. While metadoxine did not cause any effect on cell membrance properties, it showed a dose-dependent increase of mlPSCs frequency, indicating enhanced gamma-aminobutyric acid (GABA)ergic synaptic transmission via a presynaptic effect. Metadoxine did not serve as a positive reinforce.
CONCLUSIONS: The results demonstrate that metadoxine displays a novel monamine-independent mechanism of action that may be associated with synaptic transmission and cognitive regulation and may lack abuse potential in humans.
Two sentence summary: Metadoxine did not show any effect on levels of monamines measured by microdialysis, and it did not serve as a positive reinforce. These findings, combined with a novel MOA characterized by facilitation of GABAergic inhibitory transmission, provide evidence for reduced abuse potential and pro-cognitive properties.

8. ***Clinical Correlates of Working Memory Deficits: A Controlled Study of Children with and without ADHD***

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BACKGROUND: Major sources of morbidity and disability in ADHD are deficits in executive functions, of which the ability to hold information in memory for short time periods (working memory, FKA freedom from distractibility) is a prominent component. The main aim of this analysis was to clarify the implications of such deficits among youth with ADHD.
METHODS: Subjects were youth with (N=259) and without (N=222) ADHD ascertained from pediatric and psychiatric clinics. Assessments included measures of psychiatric, psychosocial, educational, and cognitive functioning. Subjects were split into four groups: subjects with ADHD and FFDD (ADHD+FFDD), subjects with ADHD and no FFDD (ADHD), subject with FFDD and no ADHD (FFDD + Controls), and subjects with no FFDD and no ADHD (Controls).
RESULTS: Significantly more youth with ADHD had freedom from distractibility deficits (FFDD) than controls. ADHD with FFDD was associated with an increased risk for grade retention and a decrease in academic achievement relative to ADHD alone, controlling for SES, learning disabilities, and IQ. No differences were noted in social functioning or psychiatric comorbidity.

CONCLUSIONS: Youth with ADHD and FFDD are at high risk for significant impairments in academic functioning. These results support screening children with ADHD for Working Memory deficits so that interventions can be implemented to prevent academic failure.

9. ***Further Evidence that Severe Scores in the Aggression/Anxiety-Depression/Attention Subscales of Child Behavior Checklist (Severe Dysregulation Profile) Can Screen for Bipolar Disorder Symptomatology: A Conditional Probability Analysis***

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BACKGROUND: Previous work shows that children with high scores (2 SD, combined score ≥ 210) on the Attention Problems, Aggressive Behavior, and Anxious-Depressed (A-A-A) subscales of the Child Behavior Checklist (CBCL) are more likely than other children to meet criteria for bipolar (BP)-I disorder. However, the utility of this profile as a screening tool has remained unclear.
METHODS: We compared 140 patients with pediatric BP-I disorder, 83 with attention deficit hyperactivity disorder (ADHD), and 114 control subjects. We defined the CBCL-Severe Dysregulation profile as an aggregate cutoff score of ≥ 210 on the A-A-A scales. Patients were assessed with structured diagnostic interviews and functional measures.
RESULTS: Patients with BP-I disorder were significantly more likely than both control subjects (Odds Ratio [OR]: 173.2; 95% Confidence Interval [CI], 21.2 to 1413.8; $P < 0.001$) and those with ADHD (OR: 14.6; 95% CI, 6.2 to 34.3; $P < 0.001$) to have a positive CBCL-Severe Dysregulation profile. Receiver Operating Characteristics analyses showed that the area under the curve for this profile comparing children with BP-I disorder against control subjects and those with ADHD was 99% and 85%, respectively. The corresponding positive predictive values for this profile we 99% and 92% with false positive rates of < 0.2% and 8% for the comparisons with control subjects and patients with ADHD, respectively.
LIMITATIONS: Non-clinician raters administered structured diagnostic interviews, and the sample was referred and largely Caucasian.
CONCLUSIONS: The CBCL-Severe Dysregulation profile can be useful as a screen for BP-I disorder in children in clinical practice.

10. ***Assessing Validity of "age of onset" Criteria for Diagnosis of ADHD in DSM-5***

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OBJECTIVE: Convincing data about the age of onset criterion for diagnosing ADHD in DSM-IV led to the increase in age of onset to twelve in DSM-V. The present work attempted to clarify the validity of ADHD when diagnosticians cannot establish an onset prior to the DSM-V criterion of age twelve.

METHOD: We addressed the validity of DSM-V's age at onset criteria by comparing three groups of adults: a) Full ADHD subjects met all DSM-V criteria for childhood onset ADHD (N=182); b) Late-Onset ADHD subjects met all criteria except the age at onset criterion (N=17), and c) non-ADHD subjects did not meet any of the above criteria (N=117). We hypothesized that Late Onset ADHD would show patterns of symptoms, psychiatric comorbidity, functional impairment, familial transmission, quality of life measures, social adjustment and intelligence levels similar to that seen for Full ADHD subjects.
RESULTS: Full ADHD had more inattentive symptoms, scored more on sense of well-being, overall life satisfaction and functioning in daily life measures in quality of life assessment scale, and had a lower social adjustment scores compared to Late-onset ADHD subjects. Both groups had similar patterns of psychiatric comorbidity, functional impairment, familial transmission and intelligence.
CONCLUSIONS: Our data suggests comparable clinical features and co-morbidities in Full-ADHD and Late onset ADHD groups when applying DSM-V's age of onset criteria. Our results suggest that Late-Onset adult ADHD is still valid even after discarding the DSM-V age of onset criterion.

11. ***Resting Functional Connectivity in Children with Attention Deficit/Hyperactivity Disorder (ADHD)***

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Attention deficit/hyperactivity disorder (ADHD) is one of the most prevalent neuropsychiatric disorders among children. Although the clinical presentation and treatment of ADHD are well established, its etiology is not yet known. Recent functional neuroimaging techniques may help increase knowledge about the pathophysiology of the disorder, allowing for the empirical testing of theoretical hypotheses on brain networks in ADHD. In this study, we analyzed a group of 23 treatment naïve boys with ADHD, aged between 8 and 10 years old, who underwent a protocol of resting-state functional magnetic imaging before and after six months of treatment with methylphenidate. Functional connectivity in the default mode network (DMN) was assessed before and after treatment using regions of interest (ROI) and independent component analysis (ICA). Results of the seeds analysis showed no significant changes in connectivity between regions of the DMN following treatment, with a relatively small increase in the anterior-posterior connectivity of the network. The ICA revealed a significant increase in the connectivity between the left putamen and the DMN ($p < 0.01$, corrected). There was also a positive correlation between the decrease of symptoms and the connectivity between the putamen and the DMN after treatment ($rho = -0.65$, $p = 0.017$). These findings suggest that treatment with methylphenidate might modify the connectivity between the DMN and subcortical nuclei. Dysfunctions in cortical-subcortical circuits have often been associated with the pathophysiology of ADHD. The effect of treatment with methylphenidate may in part be associated with elevated dopamine levels in subcortical nuclei, modulating its connectivity with the DMN.

12. ***The Single Dose Pharmacokinetics of HLD200: A Modified Release Methylphenidate (MPH) Formulation in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD)***

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OBJECTIVE: The objective of this study was to examine safety and tolerability and to evaluate the single dose pharmacokinetics of orally administered HLD200 in the evening to children and adolescents with ADHD. The study design allowed pharmacokinetic parameters in children and adolescents to be compared.

BACKGROUND: Although several effective extended-release methylphenidate (MPH) products are available, early morning ADHD symptoms remain problematic for patients and their caregivers. HLD200 is a novel delayed and extended-release oral capsule formulation of MPH. When administered in the evening before bedtime, HLD200 is formulated to delay the initial release of MPH approximately 8-hours, coincident with the early morning pre-awakening period, in order to provide an onset of clinically significant treatment effect immediately upon awakening and throughout the patient's early morning routine. Additionally, HLD200's novel extended-release drug profile is designed to provide significant treatment effect throughout the remaining periods of the day currently targeted by conventional extended-release formulations.

METHOD: This trial was a Phase I/II, single site, open-label PK study in children and adolescents diagnosed with ADHD. A total of 29 male and female subjects (11 aged 6 to 12 years old; and 18 aged 13 to 17 years) who had previously been treated with MPH received a single oral dose of 54 mg HLD200 (equivalent to approximately 40 mg MPH *in vivo*). The study was IRB-approved and all subjects/parents provided assent/consent to participate in the trial. Screening included administration of the MINI International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) to confirm ADHD Diagnosis, physical exam, ECGs, collection of laboratory data and urine drug screen. Subjects were required to discontinue ADHD treatments for at least five days prior to dosing with HLD200.

Eligible subjects were admitted to the study facility at approximately 3 PM prior to dosing and remained there until approximately 9 PM the next day. After an updated medical history, drug screen, ECGs and physical exam, eligibility was confirmed. A catheter was then inserted and pre-dose labs and PK samples were collected. HLD200 (54 mg) dosing occurred at approximately 9 PM. Subjects consumed a low fat meal approximately four hours prior to dosing. After an overnight fast, subjects were encouraged to eat meals and snacks and to stay well hydrated in order to improve tolerability to PK sampling.

PK samples (4mL) were collected prior to dosing (t=0) and following dosing at t=4, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, 24, 36 and 48 hours to determine plasma MPH concentration. Vital signs were collected prior to each PK draw and multiple electrocardiograms were collected during the trial.

Plasma samples were analyzed by MPH in plasma using high performance liquid chromatography with Tandem Mass spectrometry (LC-MS/MS). Overall, the inter-assay precision (%CV) and accuracy (%Bias) ranged from 1.6% to 2.7% and from –2.9% to 3.4%, respectively.

RESULTS: Plasma MPH parameters are shown in the Table 1 below. Mean values of body weight-adjusted maximum plasma concentration (Cmax), time to maximum plasma

concentration (Tmax) and area under the concentration-time curve (AUC) were similar among children and adolescents. The concentration-time profile of HLD200 is depicted graphically in Figure 1 and Figure 2 (dose-body weight corrected). As would be expected, variability in drug exposure between children and adolescents appears to be due to weight differences; as weight corrected values are very similar between the two groups. There were no serious adverse events (AEs) and the most common treatment emergent adverse events (TEAEs), thought to be possibly or probably drug-related, were those predictably reported with MPH. These AEs were mild and included upper abdominal pain (2 occurrences), intermittent headaches, emesis and flatulence (one occurrence each). Although the subjects were awakened to obtain PK samples, there were no reported spontaneous difficulties with appetite, sleep latency, middle of the night awakenings, or early morning awakenings.

Table 1: Mean (SD) Plasma Methylphenidate Pharmacokinetic Parameters in Children and Adolescents with ADHD following a Single Oral 54 mg dose of HLD200

PK Parameter	**6-12 years (N=11)**	**13-17 years (N=18)**
Mean C_{max} (ng/mL) ± CV%	11.4 ± 36.3	7.17 ± 23.7
Mean C_{max} (ng/mL) ± CV% (weight corrected-mg/kg)	7.44 ± 30.1	8.84 ± 34.5
Mean T_{max} (hr) ± CV%	17.7 ± 14.1	17.1 ± 14.5
T_{max} (hr) Median (range)	18.2(12.4-22.0)	16.2 (13.9-22.1)
Mean AUC $_{0-t}$ (ng/mL) ± CV%	205.5 ± 39.1	105.5 ± 30.0
Mean AUC $_{0-t}$ (ng/mL) ± CV% (weight corrected mg/kg)	129.7 ± 27.3	129.4 ± 34.8
Mean AUC $_{0-inf}$ (ng/mL) ± CV%	210.1 ± 38.5	109.6 ± 30.8
Mean AUC $_{0-inf}$ (ng/mL) ± CV% (weight corrected mg/kg)	132.7 ± 27.2	134.4 ± 35.7

Abbreviations: N= number of subjects, hr= hour, CV = coefficient of variation, C_{max} = peak plasma concentration, T_{max} = time at peak plasma concentration, AUC = area under the curve

Figure 1. Mean Observed MPH Plasma Concentration Following a Single Evening Administration of HLD200 (54 mg) in Adolescents and Children with ADHD.

13. ***Childhood-onset Adult ADHD Treated with Metylphenidate Modified Release (MPH-LA) Maintained Functional Improvement over a Period of One Year***

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INTRODUCTION AND OBJECTIVES: A previous 40-week, randomized, double-blind placebo-controlled core study comprising 3 phases (9-week dose confirmation phase, 5-week real-life dose optimization phase and 6-month maintenance of effect phase) reported that MPH-LA (40-80mg/day) in adults with childhood-onset ADHD, controlled ADHD symptoms as well as reduced functional impairment, with a good tolerability profile.[1] Herein, we report maintenance of functional improvement in MPH-LA treated adult ADHD patients from a 26-week open-label extension phase of the same study using Sheehan Disability Scale (SDS) total and subscale scores.
METHODS: All patients entering extension phase (n=298) were initiated on treatment with MPH-LA (20mg/day) that was up-titrated in increments of 20mg/week to reach individual patient's optimal daily dose of 40, 60 or 80mg. Functional improvement was determined by decrease in SDS total, subscale (work, social-life and family-life disability), days lost and days underproductive scores at the end of extension study from maintenance of effect baseline and extension baseline.
RESULTS: At the end of extension phase, mean change in SDS total, work, social-life and family-life subscale scores from maintenance of effect baseline was -1.4, -0.4, -0.4 and -0.5 points, respectively and from extension baseline was -4.8, -1.8, -1.4 and -1.6 points, respectively. Mean change in days lost from maintenance of effect baseline and extension baseline was -0.2 and -0.5 points, respectively; and in days underproductive was -0.2 and -1.2 points, respectively. The safety results were consistent with the established safety profile for MPH-LA.
DISCUSSION: In adults with childhood-onset ADHD, long-term treatment with MPH-LA maintained functional improvement.
References:

1. Huss et al. Methylphenidate hydrochloride modified-release in adults with attention deficit hyperactivity disorder: a randomized double-blind placebo-controlled trial. Adv Ther. 2014;31:44-65.

Summary: MPH-LA (40–80 mg/day) maintained a beneficial impact on work-, social- and family-life in adult ADHD patients, over a period of one year. Long-term treatment with MPH-LA in adult ADHD patients was well-tolerated.

14. ***Neurofeedback as a Non-pharmacological Treatment Option for Adult ADHD Patients in a Clinical Setting***

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INTRODUCTION: Neurofeedback is a method of training brain activity through the use of operant conditioning. Users are given continuous feedback on expressed brain wave patterns and are rewarded for expressing the desired ratio of theta/beta brainwave activity. In theory, neurofeedback will facilitate structural improvements over time such that symptoms of mental disorders like ADHD will improve. Exploring non-pharmacological treatments for ADHD may be useful if a patient wishes to avoid stimulant drugs, has developed a high tolerance of stimulants, or if there are medication-resistant residual symptoms.
METHODS: Neurofeedback was offered at a clinical practice to twelve adult ADHD patients over the course of twelve weeks. Both objective and subjective measures of ADHD symptoms were obtained prior, during and after the training.
RESULTS: At intake, patients completed multiple self-rating scales (CAARS, BDEFS, SWAN) and one computer test of attention (ANT); of these, only CAARS and BDEFS self-report were correlated. During training, both objective (results of the brain training games and subjective (BDEFS) measurements were made. Only five of the original twelve participants completed the twelve week course of neurofeedback training; exit interviews were done for both completers and non-completers. For completers, the BDEFS showed a general improvement in total scores over time, and brain training attention index score also improved over time. Both completers and non-completers showed improvement in reaction time and conflict scores on the ANT.

15. ***Sustained Attention Deficits in Pediatric Obsessive-Compulsive Disorder and Tic Disorders: A Comparison using the Continuous Performance Test***

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BACKGROUND: Children with obsessive-compulsive disorder (OCD) and tic disorders (TD) often have comorbid attention-deficit hyperactivity disorder (ADHD). The continuous performance test (CPT) is a computerized examination of distractability, impulsivity and sustained attention (reaction time variance). Examining deficits in sustained attention in OCD, TD or comorbid OCD+TD may explain the nature of ADHD comorbidity with these conditions. Whether sustained attention deficits are increasingly present over the 6-block CPT examination (compared to baseline 1 block) will yield information on the sustained attention capacity in children with these disorders.
METHODS: 46 children with OCD (n=19), TD (n=15) or OCD+TD (n=12) were administered the computerized Conners CPT. The children had a mean age 12.7 (3.7) years and were 72% male. A linear mixed model examined block x diagnosis effects.
RESULTS: Time and age showed significant effect compared to block overall ($p < .0001$), as well as an interaction effect for time and diagnosis in the overall model ($p = .001$). Younger participants showed significantly higher standard error. Both TD and OCD+TD showed a diagnosis x block interaction effect, with TD showing significant differences in blocks 4, 5, and 6 compared to baseline and OCD+TD showing differences in blocks 5 and 6. OCD only did not show deterioration in sustained attention over the 6 blocks.
DISCUSSION: A deficit of sustained attention is found to most notably affect those with TD only and OCD+TD, and not those children with OCD only. Future research may focus on the specificity of sustained attention deficits in OCD and TD.

16. ***Review of Atomoxetine Treatment in Adults with Attention-Deficit/Hyperactivity Disorder***

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Prevalence and natural history data suggest that up to two-thirds of children with attention-deficit/hyperactivity disorder (ADHD) will continue to manifest ADHD symptoms into adulthood. An epidemiologic, community-based study found the prevalence of adult ADHD to be 4.4%. There is growing recognition that adult ADHD can result in negative consequences for the individual including reduced socioeconomic success, functional impairment, and a diminished quality of life. ADHD is often associated with a number of comorbid psychiatric disorders, including mood and anxiety disorders and substance use disorders. Atomoxetine is a nonstimulant, selective noradrenergic reuptake inhibitor approved by the FDA for treatment of ADHD in children, adolescents, and adults on the basis of six pivotal registration studies, two of which were in adults. Many additional clinical studies have been completed that further demonstrate treatment with atomoxetine in adults with ADHD is efficacious with an acceptable safety profile. The purpose of this review is to summarize the efficacy and safety of atomoxetine treatment for adult ADHD including efficacy data in special populations such as patients with substance use disorder and anxiety disorder. We searched the databases Embase, MEDLINE, and PsycINFO using the terms “ADHD” AND “adult” AND “atomoxetine” capturing publications from 1998 to early 2014. We also address the issue of healthcare provider and patient perception of efficacy versus results of clinical trials and past experience with other ADHD medications. We will also provide a review of functional outcomes in adult patients with ADHD treated with atomoxetine. Safety and tolerability issues will also be addressed.

17. ***ADHD in Adults: Dissemination Initiative First Year Results***

Jonathan Marx
Inquill

18. ***Functional Impairment in ADHD: What Matters More, Symptoms or Personality?***

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OBJECTIVE: To examine the effect of personality traits and characteristics on quality of life and functioning, independent of attention deficit / hyperactivity disorder (ADHD) symptoms in adults with ADHD.
METHOD: Participants were adults with (n=206) and without ADHD (n=123) who completed the Temperament and Character Inventory (TCI), the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and the Social Adjustment Scale Self-Report (SAS-SR). Participants also provided information on academic, motor vehicle operation, legal, social, familial, and occupational functioning.
RESULTS: Adults with ADHD significantly differed from controls across all TCI personality domains. On average, adults with ADHD endorsed more novelty seeking, harm avoidance, and self-transcendence, and less reward dependence, persistence, self-directedness, and cooperativeness. In adults with ADHD, personality traits and characteristics significantly predicted functional impairment across several domains of life functioning, even when controlling for ADHD symptoms. Furthermore, self-directedness emerged as an especially

strong predictor of quality of life and novelty seeking emerged as an important predictor of functional impairment.
CONCLUSIONS: In adults with ADHD, personality factors exert unique effects on quality of life and functional impairment across major life domains, beyond the effects expected and associated with ADHD symptoms alone. Improving self-directedness in adults with ADHD may lead to improvements in quality of life and reductions in functional impairment.

19. ***A Population-based PK/PD Analysis of Dasotraline Efficacy in the Treatment of ADHD in Adults***

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BACKGROUND: Dasotraline (SEP-225289) is a new chemical entity with a slow elimination half-life demonstrating dopamine (DAT) and norepinephrine (NET) transporter inhibition in clinical studies. Here we hypothesized dasotraline plasma concentrations, measured in an efficacy trial of adult ADHD, would be correlated with improvements in ADHD RS-IV across subjects, treatment groups, and visits. METHODS: Plasma concentrations of dasotraline from a total of three Phase 1 studies and two Phase 2 studies were analyzed by population PK methodology. A 1-compartment population PK model with sequential zero-order followed by first-order absorption and dual (nonlinear and linear) elimination described dasotraline PK across a total of 395 subjects after single or multiple dose administrations ranging from 0.2 to 36 mg. Norepinephrine metabolite DHPG concentrations from 329 subjects were modeled as a power function of the time-matched dasotraline concentrations as derived from the PK model. Population PK/PD modeling of dasotraline concentrations (Cav) used a sigmoid Emax time-course model.
RESULTS: Population PK model adequately predicted dasotraline concentrations; steady-state was attained by 2 weeks with a mean apparent half-life of 47 hours. Concentrations of the norepinephrine metabolite DHPG indicated central NET inhibition was achieved within the first days of dosing. An exposure-response relationship was found between increases in Cav, Emax and reductions in ADHD RS-IV. DISCUSSION: These results demonstrate a dose- and concentration-response relationship of pharmacological activity in ADHD, supporting the concept that maintaining constant, steady-state inhibition of both dopamine and norepinephrine transporters is a novel pharmacological approach to the management of ADHD symptoms.
2-sentence summary:
Dasotraline is a potent inhibitor of dopamine and norepinephrine transporters characterized by a slow elimination half-life in humans. The population PK/PD analysis of a Phase 2 efficacy trial in adult ADHD support the concept that maintaining constant, steady-state inhibition of both dopamine and norepinephrine transporters is a novel pharmacological approach to the management of ADHD symptoms.

20. ***Dasotraline in the Treatment of Adults with Attention-Deficit/Hyperactivity Disorder: A Randomized, Double-blind, Placebo-controlled Proof of Concept Trial***

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BACKGROUND: Dopamine and norepinephrine are associated with the pathophysiology of ADHD, and drugs that facilitate synaptic concentrations of dopamine and norepinephrine are clinically useful in the pharmacological management of ADHD symptoms. Dasotraline (SEP-225289) is a new chemical entity with clinical demonstration of dopamine (DAT) and norepinephrine (NET) transporter inhibition. Unique relative to current medications, dasotraline's slow elimination half-life was hypothesized to provide therapeutic benefit throughout the 24-hour dosing interval.
METHODS: Dasotraline doses were selected to maintain, throughout the 24-hour dosing interval, steady-state plasma concentrations above 4 ng/mL, corresponding to expected DAT and NET inhibition above 50%. Adults (age 18-55, N=341) with ADHD (DSM-IV-TR criteria) were randomized in a double-blind fashion 1:1:1 to fixed doses of dasotraline 4 mg/day, 8 mg/day, or placebo for a 4-week treatment period (NCT01692782).
RESULTS: The reduction in ADHD RS-IV with adult prompts total score was statistically significant for dasotraline 8-mg (MMRM LS mean difference = -4.18, adjusted p=0.019) with a strong trend for 4-mg (-2.68, p=0.076) compared with placebo at the 4-week endpoint. Both 4-mg and 8-mg demonstrated clinically meaningful and statistically significant reductions in CGI-S scores compared with placebo (p=0.021, p=0.013, respectively, at Week 4). The most frequent adverse events reported were insomnia, decreased appetite, nausea, and dry mouth, consistent with DAT/NET pharmacology. Discontinuations due to adverse events were 1.8%, 11.2% and 29.7% of subjects in placebo, 4-mg and 8-mg groups, respectively.
DISCUSSION: Dasotraline demonstrated statistically and clinically meaningful effects in adults with ADHD, further investigation is warranted in both adult and pediatric populations.
2-sentence summary:
Dasotraline is a new chemical entity with activity at both dopamine and norepinephrine transporters. A clinical study in adults with ADHD demonstrated statistically and clinically meaningful effects, suggesting that constant, steady-state inhibition of both DAT and NET is a novel pharmacological approach to the management of ADHD symptoms.

21. ***Attention-Deficit/Hyperactivity Disorder with Sluggish Cognitive Tempo is Associated with Internalizing Disorders and Executive Function Deficits in Adults***

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Objectives: Sluggish Cognitive Tempo (SCT), has been proposed to better characterize a subset of those with ADHD and attention and concentration problems. We sought to characterize adults with ADHD and SCT with respect to internalizing disorder comorbidity, executive function deficits, association with ADHD subtype, and processing speed. Methods: For this retrospective, observational, 115 subjects with ADHD aged 18–66 completed clinical rating scales and a clinical interview. Correlations were calculated between SCT scores and Beck Depression Inventory II (BDI-II), State-Trait Anxiety Inventory (STAI), and Barkley Deficits in Executive Function (BDEFS) scales. Results: The sample included 43 (37 %) ADHD-combined and 68 (59%) ADHD-inattentive. Fifty-five (48%) were classified as high SCT, 41 (36%) had a depressive disorder and 31 (27%) an anxiety disorder. Depression and anxiety rating scale scores correlated significantly with total SCT score. SCT total score correlated positively with three BDEFS subscales after partialling out the contributions of internalizing disorders and ADHD

severity. No relationship was observed between SCT and ADHD subtype, WAIS processing speed or full scale IQ. Conclusions: SCT is not merely a proxy for internalizing symptomatology. SCT scores are associated with independent executive function deficits above and beyond those associated with ADHD symptoms. SCT did not specifically differentiate ADHD-I from ADHD-C in adults, nor was SCT specifically linked to slow processing speed.

22. ***Mixed Amphetamine Salts- Extended Release for Attention Deficit/Hyperactivity Disorder (ADHD) Adults with Cocaine Use Disorder***

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Aims: Methylphenidate has produced modest effects in reducing ADHD symptoms in those with substance use disorders, and the impact of treating ADHD on substance use remains unclear. There are no controlled published studies evaluating amphetamine analogues. The purpose of this 13-week double-blind, placebo-controlled trial two-site study was to evaluate the efficacy of two robust doses of mixed amphetamine salts-extended release (MAS-ER; Adderall-XR®) as a treatment for ADHD and cocaine dependence.
Methods: 126 ADHD adults with cocaine dependence were randomized to an active medication dose (60 or 80 mg of MAS-ER a day) or placebo. Participants had to meet DSM-IV criteria for adult ADHD and cocaine dependence. Participants were titrated up to 60 mg/day or 80 mg/day of MAS-ER and maintained on this dose for 11 weeks. All patients received weekly individual cognitive behavioral therapy.
Results: The randomized sample was predominantly male (84%) and 57% White, 17% Hispanic, and 17% African-American. Seventy-five percent of the sample were retained through the end of the maintenance phase (week 13), with no group differences. The primary ADHD outcome measure, $\geq$ 30% reduction in ADHD symptoms from last week in trial to baseline, was significantly different across the 3 study groups (p=.0046) with the greatest difference between the 60 mg and placebo groups (p=.0018). Notably, covarying for baseline cocaine use, the proportion of cocaine positive weeks on average over the study's duration was significantly different across the 3 study groups (p = .0051) with the 80 mg MAS-ER producing significant less cocaine positive weeks than the placebo arm (p=0.0009) and less cocaine positive weeks than the 60 mg arm (p=0.08). There were 2 serious adverse events, neither was deemed medication related.
Conclusion: This is the first pharmacotherapy trial evaluating and demonstrating an amphetamine analog for adults with ADHD and cocaine dependence. These preliminary data suggest that high dose MAS-ER is well-tolerated and is superior to placebo in reducing both ADHD symptoms and cocaine use.
Supported by NIDA Grants: RO1 023652, K02 00465, and K24 029647

23. ***Slow Learning Pattern in Risk Selection Process in Adolescents with ADHD***

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Introduction: Recent focus ADHD has been placed in adolescence as one of the most important stages for this disorder. At these ages the influence of behavioral difficulties and comorbidity reaches the highest severity and effect. To date there are few studies on the development of

executive function in adolescents with ADHD, and even less studies on sensitivity to risk-choice. Objective: to evaluate and describe the performance in risk- detection, and risk-benefit processing in adolescents diagnosed with ADHD. Method: 35 ADHD-adolescents (age-average: 13.49) with normal level of intelligence and 26 paired controls participated. Tests: Iowa-type developmental-variant test. Comparisons: ADHD versus control group without ADHD using t tests, a block by block performance was analyzed using ANOVA. Results: ADHD adolescents presented lower ability to detect risk selections (avoid risk-bad choices): ADHD 40.34 (8.5), controls 33.31 (3.4); and a lower risk-benefit processing capacity (approach good-benefit choices): ADHD 21.74 (9.5), controls 30.43 (11.3), t test p= .001. The main finding was that ADHD-adolescents presented a slower learning pattern to avoid risk choices (they took more trials to identify-avoid risk choices). The ADHD-group initially (block 1) selected more risk-cards and maintained a higher risk-cards selection than the control group until block 2; it was until block 3 when the performance in both groups became similar. Conclusions: literature is scarce concerning studies with Iowa-type paradigm in pure adolescent samples. Learning patterns in ADHD represent a new field of analysis-intervention. Emphasis should be place in executive functions development in adolescents with ADHD to prevent risk-choices.

24. ***Emotional Bias of Cognitive Control in Adults with Childhood Attention-Deficit/Hyperactivity Disorder***

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Affect recognition deficits found in individuals with attention-deficit/hyperactivity disorder (ADHD) across the lifespan may bias the development of cognitive control processes implicated in the pathophysiology of the disorder. This study aimed to determine the mechanism through which facial expressions influence cognitive control in young adults diagnosed with ADHD in childhood. Fourteen probands with childhood ADHD and 14 comparison subjects with no history of ADHD were scanned with functional magnetic resonance imaging while performing a face emotion go/no-go task. Event-related analyses contrasted activation and functional connectivity for cognitive control collapsed over face valence and tested for variations in activation as a function of face valence. Probands with childhood ADHD made fewer correct responses and inhibitions overall than comparison subjects, but showed comparable effects of face emotion on response execution and inhibition. The two groups showed similar frontotemporal activation for cognitive control collapsed across face valence, but differed in the functional connectivity of right dorsolateral prefrontal cortex, with fewer interactions with subgenual cingulate cortex and ventrolateral prefrontal cortex in probands than comparison subjects. Further, valence-dependent activation for response execution was seen in amygdala, ventral striatum, subgenual cingulate cortex, and orbitofrontal cortex in comparison subjects but not probands. The findings point to functional anomalies in limbic networks that could impact cognitive control in emotional contexts and may contribute to the social and emotional problems associated with ADHD.

25. ***A Pilot Study of a Novel Monoamine Triple Reuptake Inhibitor Centanafadine (EB-1020) SR in the Treatment of ADHD in Adults***

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BACKGROUND**:** This pilot study was designed to evaluate Centanafadine (EB 1020)-SR as a novel non-stimulant treatment option for adult attention-deficit hyperactivity disorder (ADHD). Centanafadine-SR is a norepinephrine-preferring triple reuptake inhibitor with IC_{50} values for transporter reuptake inhibition of 6 nM, 38 nM, and 83 nM ,for norepinephrine, dopamine and serotonin respectively. *Methods***:** A total of 41 adult males with well-characterized ADHD enrolled in this 4-week, single-blind study with 1-week placebo run-in. Centanafadine-SR was given twice daily and titrated to a target dose of 500 mg daily over 7 days. Outcomes assessed included ADHD, executive functioning, and tolerability.
RESULTS: 37 subjects completed the trial. Centanafadine-SR produced a 21-point reduction on the ADHD Rating Scale-IV (endpoint mean score =17, $p<0.0001$) including significant reductions in inattentive ($p<0.0001$) and hyperactive impulsive symptoms ($p < 0.0001$). Overall, 68% of subjects were considered responders using the Clinical Global Impression of Improvement (much/very much improved). Clinically and statistically significant improvements in overall and specific domains of executive function using the Behavioral Inventory of Executive Functioning were also found (overall $p<0.0001$). No clinically meaningful trends in adverse events, laboratory values, vital signs, or ECG parameters were noted.
CONCLUSIONS: Centanafadine-SR appears effective in treating ADHD and executive functioning deficits in adult males. The maximum dose studied appears to be well tolerated. Based on these results, randomized, controlled studies of EB 1020 appear warranted.

26. ***Looking Into the Eye of ADHD - First Data on Photophobia in Adults with ADHD***

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Background: Many adults with Attention-Deficit Hyperactivity Disorder (ADHD) wear sunglasses, also on cloudy days and in winter. Asking about this behaviour, they say they are oversensitive to light. This seems problematic because of the high prevalence of Delayed Sleep Phase Syndrome (78%) in adults with ADHD 4. By wearing sunglasses, during daytime little light may reach their eyes, limiting even further synchronisation of the biological clock to time of the day.
Aim: To gain more insight into the associations between possible eye dysfunctions and photophobia, and the relationship with the delayed circadian rhythm in adults with ADHD.
Methods: Overview of the literature and first data of a short online survey on the oversensitivity to light in adults with ADHD compared to controls.
Results:
Literature

- In 70-80% of children with ADHD there are difficulties with visual acuity or with the visual system [1].
- In children, visual acuity problems diminish with ADHD medications [3].
- Adults with ADHD also report visual impairments [2.].
- The visual problems may correlate with the delayed circadian rhythm in adult ADHD [4].

Online survey

- N=495, of which 47% had self-reported ADHD (symptoms), and 53% were controls.
- Of those with ADHD (symptoms), 69% reported oversensitivity to light, versus 28% of controls (Table 1), which was controlled for photophobia during episodes of migraine.
- People with ADHD also reported to wear sunglasses significantly longer in every season as compared to controls (Figure 1).
- After controlling for migraine, oversensitivity to light was associated with ADHD, age, eye problems, wearing glasses or eye lenses, and with chronic fatigue, but not with a delayed sleep phase.

27. ***Mediated Moderation of ADHD: Role of ODD and Mood Lability in Treatment***

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Introduction: 40 - 60% of youth with ADHD have co-occurring Oppositional Defiant Disorder (ODD). We therefore examined the impact of ODD on treatment of youth with ADHD.
Methods: 216 youths with ADHD, any subtype, ages 6 to 17 years, were treated with either ATX or MPH as part of a larger clinical comparator trial. Data from the Kiddie SADS-PL, Conners Parent Rating Scales, and parent ratings of mood lability were analyzed to: 1) examine change in ODD symptoms by drug and ADHD severity; 2) examine moderated mediation of ADHD response by drug and ODD; and 3) examine mood lability x ODD x drug interactions.
Results: 84 (39%) subjects were diagnosed with comorbid ODD; 132 (61%) had ADHD only. Youth with ADHD+ODD had higher baseline ADHD-RS Total scores than youth with ADHD-ODD, showed less improvement in ADHD symptoms with treatment, and remained more impaired on their optimized drug dose. There was a trend for improvement in ADHDRS-Total score as a function of baseline ODD symptoms, and ODD symptoms moderated ADHD response (with greater improvement on MPH than ATX).Mood lability was highly associated with ODD at both baseline and on best dose. Mood Lability improved with treatment
Discussion: Youth with ODD comorbidity have significantly higher ADHD symptom severity and show less improvement in response to treatment, regardless of the treatment administered. ODD symptom severity predicted ADHD treatment outcomes with a small preference for MPH over ATX. Mood lability was highly correlated with ODD symptoms, and predicts change in ODD symptoms with treatment.

28. ***Prevalence of Attention-Deficit/Hyperactivity Disorder (ADHD) and Trauma in Latino Mothers of Youth with ADHD: Dyadic Complications and Treatment Implications***

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Introduction: There is a dearth of research examining ADHD within the Latino community. Our objective was two-fold: 1) to determine incidence and prevalence of ADHD and co-morbidity among mothers of children in psychiatric care, and 2) to characterize potential, unidentified clinical needs disparities between Latino and non-Latino mothers in an under-served community.
Methods: A licensed psychiatrist assessed 50 biological mothers of youth treated for ADHD at the Child and Adolescent Family Outpatient Clinic of the Icahn School of Medicine at Mount Sinai. This was not a treated sample, but were expected to be enriched for ADHD, as ADHD is heritable. The assessment battery consisted of the Mini-6 Neuropsychiatric Interview, Conners Adult ADHD Scale (CAARS), Adult Investigator Symptom Report Scale (AISRS), Adult Self Report Scale V 1.1 (ASRS), ADHD Clinical Diagnostic Scale (ACDS), Wechsler Abbreviated Scale of Intelligence (WASI), Behavior Rating Inventory of Executive Functioning – Adult Self-Report version (BRIEF-A), and direct measures of gross motor activity, impulsivity, inattention, and response inhibition as measured by the Quotient.
Results: 27 Latino and 23 non-Latino mothers were evaluated for ADHD and other disorders. 78% (n=21) of Latino mothers met diagnostic criteria for ADHD. 55% (n=12) of the non-Latino mothers met these diagnostic criteria. Trauma contributed to the large disparity and was greatly elevated among this population of Latino mothers (55%, n=15) as compared to our non-Latino mothers (30%, n=7).
Discussion: ADHD was enriched in our sample, and Latino mothers were disproportionately affected by trauma-related symptoms. There was a robust disparity between the two groups, despite the small sample, indicating need for larger studies to assess, characterize and treat these under-served women.

29. ***Methylphenidate and Atomoxetine Effects on Weekday and Weekend Sleep***

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Background: Sleep problems are extremely common in children receiving psychopharmacologic treatment. Previous studies have reported an association between stimulant medication and increased sleep onset latency.
Objective: We compared parental perceptions of sleep problems during weekdays and weekends in children treated to an effective dose of methylphenidate (OROS MPH) vs. atomoxetine (ATX), controlling for age and gender.
Design/Methods: A previously validated, parent completed rating scale was administered at baseline, and at end of treatment (EOT) evaluations to participants in the Methylphenidate-Atomoxetine Crossover (MACRO) Study, a 2-site, double-blind, comparator trial of methylphenidate and atomoxetine (ATX) employing a flexible dosing titration in 230 children and adolescents. Regression models utilizing subject as a fixed effect were used to compare differences in sleep outcomes between MPH and ATX.
Results: Sleep problems occurred in 21% of the participants. The most common sleep problems reported at baseline were: takes more than 30 minutes to fall asleep 23.9%, grinds teeth 19.3%, snores 16.4%, too much energy to sleep 13.4%, talks in sleep 11.7%, and excessive movements in sleep 10.5%. When comparing the effects of MPH (mean dose = 51.3 mg SD 17.8) at end of treatment to ATX (mean dose = 1.3 mg, SD 0.5) differences were most pronounced when examining weekend sleep as opposed to week day sleep.

Insomnia was worse on MPH relative to ATX (p = 0.01). Weekend sleep duration was greater on MPH compared to ATX.
This is in large part because weekend wake times were 0.21 hours later (95%CI 0.07 – 0.34) on MPH (8:48 AM) than on ATX (8:35 AM).
These effects were especially pronounced in girls (increase of 0.33 hours, 95%CI 0.10 – 0.56).
Conclusions: Children with ADHD displayed frequent sleep problems at baseline, especially difficulty falling asleep and tiredness during the day. We observed increased weekend sleep duration, especially for girls, during their MPH treatment compared to their ATX treatment. While some children may have more challenges with sleep onset while on MPH than on ATX, once asleep they may sleep for greater total duration on weekends when there may be less external constraints on wake times. This study highlights the importance of examining weekend sleep separately from weekday sleep, and raises questions about the characteristics of "weekend catch-up sleep" among ADHD youth.

30. ***A Phase-2 Pharmacokinetic Study of a Modified Release Formulation of Dextroamphetamine Following Evening Administration to Adolescents and Children with ADHD***

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Attention Deficit Hyperactivity Disorder (ADHD) is a common childhood disorder that can persist throughout adolescence and adulthood. Stimulants are the most commonly prescribed medications for ADHD treatment. Despite improvements with drug delivery systems of the ADHD medications, early morning functioning (EMF) remains an issue in many children with ADHD.[1] A novel drug delivery system, HLD100, has been developed with delayed- and extended-release characteristics, enabling night time dosing of dextroamphetamine (d-amphetamine) to provide meaningful control of ADHD symptoms immediately upon awakening and throughout the day. Five different delayed- and extended-release formulations of HLD100 were initially developed. A study of HLD100 previously conducted in normal adult volunteers resulted in three of these candidate formulations being selected for further evaluation in adolescent and pediatric patients. These three formulations were considered in the present study.
Objectives: The primary objective of this study was to evaluate the single-dose pharmacokinetics of up to 3 test formulations of HLD100, administered in the evening to children and adolescents with ADHD. The study design allowed pharmacokinetic parameters in children and adolescents to be compared. Safety and tolerability was also assessed.
Methods: This trial was a Phase 2, single site, open-label PK study in children and adolescents diagnosed with ADHD. The study was conducted in two stages, the first involving administration to adolescents and the second to children. Main inclusion criteria for the study were male and female adolescents (ages 12-17) and children (ages 6-11) with ADHD diagnosis confirmed on Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS). Plasma sampling was performed at time zero and for 48 hours (16 total samples). The analysis of d-amphetamine in plasma was performed by LC-MS/MS. Patients received a single treatment of B-HLD100 (15 or 25 mg, dependent on medication dose level at which ADHD symptoms were controlled at enrollment). Drug administration was at 9 p.m. in the evening. The primary study

endpoint was to evaluate the safety and pharmacokinetics of HLD100. Specifically, the rate and extent of d-amphetamine pharmacokinetics as measured by AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, absorption lag time, λz, and $t_{1/2elim}$ and Adverse Events were assessed.
Results: Based on the favourable pharmacokinetic profile of the first formulation evaluated (B-HLD100), subsequent formulations were not assessed in this phase 2 study. Twenty-two subjects were enrolled including 10 adolescents and 12 children. Exposure for HLD100 was higher for children or adolescents dosed at 25 mg compared with those dosed at 15 mg. For adolescents and children, there was a delay of approximately 8 hours before HLD100 plasma levels could be measured. For adolescents, the peak plasma concentrations in terms of the median T_{max} occurred at approximately 18 hours (15-20) after administration and for children at approximately 18 hours (15-24) after administration. Mean dose body weight normalized C_{max} (in (ng/mL)/[mg/kg]) was 85.47 in adolescents and 83.34 in children. Mean dose body weight normalized AUC_{0-t} and AUC_{0-inf} for adolescents vs. children (in (ng/mL)/[mg/kg]) was 1815.9 vs. 1913.8 and 2104.4 vs. 2172.2, respectively. Weight corrected differences in the pharmacokinetic performance of the formulation between adolescents and children were considered unlikely to be of clinical significance.
In the adolescent safety analysis set, there were three AEs experienced by three subjects within the population of ten (30%). All AEs were mild in severity and judged to be unlikely or not related to study drug treatment. There were no serious or severe AEs reported in this population, and none of these participants experienced an AE leading to death or study withdrawal. There were no AEs reported in the pediatric safety analysis set of 12 subjects.
Conclusions: Following evening dosing, B-HLD100 exhibited an approximate 8-hour delayed d-amphetamine release profile, as designed, and was well-tolerated. When body weight was taken into consideration, there was no evidence of a significant difference in the d-amphetamine drug exposure profile between children and adolescents. Peak drug exposure was at approximately 3 p.m., approximately 18 hours from the 9 p.m. evening dose administration. Dose body weight normalized PK parameters were considered equivalent between adolescents and children. AEs were mild in adolescents and unlikely related to treatment, and no AEs were reported in children. Evening dosing of B-HLD100 to adolescents and children provided a pharmacokinetic profile that would allow for meaningful control of ADHD symptoms in the immediate post-waking morning period and throughout the day.
Bibliography: Whalen CK, Henker B, Jamner LD, et al. Toward mapping daily challenges of living with ADHD: maternal and child perspectives using electronic diaries. *J Abnorm Child Psychol*. 2006;34(1):115-130.

31. ***Are There Different Classes of Children with Oppositional Defiant Disorder?***
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Statement of the Problem: We previously reported that ODD has a single underlying factor, but we did not address the question whether children with ODD are a homogenous class. It is proposed by some researchers (1, 2) that children with ODD fall into different classes with differentiated concurrent and future symptoms. In particular, it is proposed that there are distinct *Irritable* and *Headstrong* classes.
Methods: The participants were 2,566 children who had SNAP-IV Parent Ratings. We selected the subset of 8 items assessing ODD (Q21 – Q28). We plotted a heat map of children responses,

to visually examine whether it would resemble a prototype with distinct types. Successive models from 1 to 5 ODD classes were fit to the data using Latent Class Analysis (LCA). We entered ADHD severity, child gender, and age as predictors of class membership.
Results: LCA produced profile plots that were parallel and distinguished only by the mean level or frequency of high symptoms, using ordinal and dichotomous indicators respectively. Using ordinal indicators, the two-class model had a satisfactory fit to the data, $L^2 = 632$, $p = .07$. Higher ADHD symptoms predicted membership in the elevated ODD symptoms class. Child gender and age were not significantly associated with class membership.
Conclusion: Our analysis supports the interpretation that the 8 ODD diagnostic items distinguish children *High* and *Low* in ODD symptoms but not distinct *Irritable* and *Headstrong* subtypes. Our results should be considered tentative and replication in different samples is necessary.
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32. ***Understanding ODD as a Disorder of Emotional Regulation and the Psychometric Properties of an Emotional Dysregulation Scale to Better Measure Emotional Regulation in ADHD and ODD***

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Statement of the Problem: Factor analyzing the SNAP-IV scale revealed that ODD is a unidimensional construct whose items group together with emotional dysregulation problems including sudden mood changes and irritability. There is a scarcity of clinical tools available to evaluate this problem. The objective of this project is to develop an instrument measuring Emotional Dysregulation.
Methods: The participants were 3,374 children for whom Parent and Teacher ratings for the SNAP-IV were available. A subset of 300 was randomly selected for Rasch Analysis. 18 questions from the SNAP-IV that loaded on an Emotional Dysregulation factor in previous work were submitted to Rasch Analysis. Rasch analysis shows how well a set of questions distinguishes levels of a trait among people. A subset of questions was selected based on Rasch Fit Indices.
Results: The 8 items satisfying our criteria were:

1. Often argues with adults
2. Often actively defies or refuses adult requests or rules
3. Often touchy or easily annoyed
4. Often is spiteful or vindictive
5. Often is quarrelsome
6. Often is negative, defiant, disobedient, or hostile towards authority figures
7. Often changes mood quickly and drastically

8. Often is irritable

The scale reliability was .98. The set of 8 questions was sufficient to distinguish children high and low in emotional regulation (person separation: 2.61).
Conclusion: Emotional Regulation has a major impact on the outcome of ADHD. In the DSM-V, irritability is associated with ODD and Disruptive Mood Dysregulation Disorder (DMDD). There is a need for a scale to measure Emotional Dysregulation in children and adolescents. Current scales are subject to significant limitations in construction and development. This scale allows for a measurement of Emotional Dysregulation.

33. ***Chart Review Study of the Relationship of Adult ADHD and Cognitive Distortions***

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Background: Targeting negative thoughts, or cognitive distortions, is considered an important factor in effective cognitive-behavioral therapy (CBT) for adults with ADHD. Although, central to most CBT programs (Ramsay & Rostain, 2015; Safren et al., 2005; Solanto, 2010), until recently, limited empirical research existed to inform clinicians about the relationship between adult ADHD and cognitive distortions (Knouse et al., 2013; Mitchell et al., 2013; Torrente et al., 2014). Thus, ongoing research that identifies the nature of the relationship between adult ADHD, cognitive distortions, and comorbid psychopathology helps further understanding of the clinical presentation of adults with ADHD and to guide interventions.
The present study was conducted to examine the relationship between adult ADHD, cognitive distortions, and comorbid psychopathology in a clinical sample. Previous research findings provide evidence of a relationship between cognitive distortions and a variety of Axis I and Axis II disorders (Rosenfield, 2004). Nonetheless, there has been much less research on the relationship between cognitive distortions and ADHD. Consequently, the goal of the current study is to further explore the nature of the relationship between adult ADHD and cognitive distortions considering that CBT is considered the psychosocial treatment of choice for adult ADHD.
Methods: Archival data were gathered from the charts of 44 adults who participated in assessment and/or treatment at a specialty outpatient adult ADHD treatment and research center in a northeastern city. Data from 44 charts were reviewed and 30 met criteria for inclusion in the study. A correlational research design was used to explore the relationship between ADHD, cognitive distortions, mood disorder symptoms, and anxiety. The frequency of endorsement of specific classes of cognitive distortions was drawn from subscales of the ICD.
Results: The results indicated a significant direct relationship between ADHD and cognitive distortions ($r = .487$, $p = .006$). The results from a follow-up exploratory analysis with a scale sensitive to primary inattentive symptoms indicated a significant, direct, positive relationship between ADHD and cognitive distortions ($r = .360$, $p = .033$). "Perfectionism" was the most frequently endorsed cognitive distortion.
Discussion/Conclusion: In line with findings from other recent studies, this study documented relationships between the distorted thought patterns that exist independent of other comorbid psychopathology in a sample of clinic-referred adults with ADHD. Moreover, "perfectionism" emerged as the most frequently endorsed cognitive distortion class.

Future studies may continue to examine different distortion profiles among adults with ADHD that help to target CBT interventions. For example, a clinically informed hypothesis is that the high rate of the "perfectionism" distortion class is associated with deficient emotional self-regulation (Barkley, 2010) insofar as adults with ADHD assume that they must "be in the mood" as a pre-condition to face difficult tasks, which translates as a situation in which there is minimal tolerance for emotional discomfort. Additionally, identification of specific cognitive distortion classes and the contexts within which they occur may enhance research on emerging CBT strategies, such as mindfulness meditation aimed at increasing tolerance for situations that evoke uncomfortable emotions related to cognitive distortions.

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34. ***Influence of Mindset on Compliance in Working Memory Training***

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Intensive computerized working memory (WM) training is currently used clinically as a mean to improve WM and attention in patients with ADHD. Due to the demanding nature of the training intervention, compliance to the protocol is often a concern and inter-individual differences are known to occur both in compliance rates and effects following the training. This study investigated how mindset and intrinsic motivation, as measured using self-rated questionnaires prior to training influence compliance to a WM training protocol. Participants (N = 112, mean age = 13) were recruited for 25 days of WM-training, 50 minutes per day over a five-week period. Mindset and intrinsic motivation prior to training was found to predict compliance to training, with an incremental mindset and higher motivation being associated with higher compliance. These results suggest that attitudes prior to WM training is important for its outcomes and can potentially explain differences in effects of training as observed between individuals for its outcomes and can potentially explain differences in effects of training as observed between individuals and between previous research studies.

35. ***A Meta-analysis Investigating the Association between ADHD and Obesity***

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AIM: The authors performed a meta-analysis of 41 studies investigating the relationship between (attention deficit hyperactivity disorder) ADHD and obesity.
BACKGROUND: ADHD is one of the most common diagnosed disorders that affects children and adults with a prevalence as high as 11% and 4.4% respectively. Clinical and epidemiological studies have implicated an association between ADHD and obesity. Studies indicate that the dopaminergic reward system may be involved in the impulsive behavior found in both ADHD and obesity. However, investigation of the neurobiological mechanism is ongoing. The prevalence of obesity in children and adult is 17% and 34.9% respectively. Obesity is a major risk factor for chronic degenerative conditions and mortality.
METHOD: This project applied random effects meta-analysis to clinical and epidemiological studies regarding ADHD and obesity. All 41 studies compared ADHD subjects to control subjects. A total of 14 analyses were performed.
RESULTS: Our main analysis used all 41 studies. We found a significant odds ratio (OR) for obesity in the ADHD subjects (OR=1.3, 95% confidence interval (95%CI): 1.2-1.5; z=4.5, $p<0.0005$). The degree of heterogeneity was high and statistically significant ($X2= 197.2$, $I2= 79.7\%$, df=40, $p<0.0005$). Additionally, Egger's test for publication bias was not significant ($t=1.8$, df=40, $p=0.08$). We will present sensitivity analyses to address the effects of outliers and covariates.
CONCLUSION: These results suggest that significant association exist between ADHD and obesity, however, future investigation is warranted.

36. ***Maintenance of Response in Attention-Deficit/Hyperactivity Disorder: What do Placebo-controlled Randomized Withdrawal Studies Tell Us?***

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37. ***Effects of Stimulants on Whole-brain Functional Connectivity in ADHD Revealed by Multivariate Distance Matrix Regression (MDMR) Analysis***

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Background: In ADHD, stimulants relieve symptoms, increase frontostriatoparietal activation and default network deactivation during inhibitory tasks, and alter intrinsic brain activity during the resting-state. We report a data-driven Multivariate Distance Matrix Regression (MDMR) analytic approach to resting-state fMRI (R-fMRI) data, investigating the effects of stimulants on whole-brain connectivity during rest in ADHD.
Methods: A high-resolution anatomic and two 6-min R-fMRI images (with/without medication) were collected in 16 adult patients with ADHD (age: 20~51y, mean: 34.3±9.3y, 11 males). The order of taking medication (11: DexmethylphenidateXR, 5: Lisdexamfetamine) was

counterbalanced (half with medication first). Head motions were matched on/off medication. MDMR analysis was performed on R-fMRI data with Medication as a within-group factor. Multiple comparisons were corrected using Gaussian random field theory ($Z>1.65$, $p<0.05$). Results: The whole-brain connectivity was altered by stimulants within the bilateral medial PFC (frontal pole, orbital FC, paricingulate gyurs, ACC), insula, precuneus/PCC, and subcortical regions (thalamus, striatum). Follow-up functional connectivity analyses were performed using local peaks of significant associations as sphere seeds (radius 3mm) to further characterize the MDMR results (the specific connections involved and directionality). The connectivity of four (out of 10) seeds was significantly affected: frontal pole, pallidum, ACC and PCC seed. The connectivity between medial visual cortex and all four seeds was greater on medication. Conclusion: The whole-brain connectivity within areas located in the frontoparietal, ventral attention, default, and limbic network is modified in ADHD by stimulants. The current work also highlights the role of medial occipital lobe in ADHD.

38. ***Concussion and mTBI***

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OBJECTIVE: Mild traumatic brain injury (TBI) (concussion) has been associated with Attention Deficit Hyperactivity Disorder (ADHD) in several ways: either as a risk factor for development of secondary ADHD or as a consequence of the increased risk taking and accidents associated with ADHD (Adeyemo BO et al. J. Attention Disorders 2014). Most of the literature on mild TBI and ADHD has examined relatively small samples of US and European young adult males. We now report an examination of the rates of ADHD and mild TBI in a large sample of Egyptian male and female athletes.
METHOD: This IRB (Cairo University, Ain Shaums) investigation involved surveying athletes in competitive representative, club sports or school sports, including: soccer, team handball, basketball and badminton. 450 athletes were surveyed over a three year period since 2011. 84% of the sample was male, 16% were female; the sample ranged in age from 14-19 y.o.. ADHD diagnosis was established on the basis of the WHO Adult ADHD Self-Report Scale v1.1 Symptom Checklist (which has been validated for adolescents and young adults) and comprehensive psychiatric interview. A history of mild TBI was established on the basis of self-report of episodes of changes in vision, changes in balance, mental reaction, sleep disturbances, dizziness, headache, vision issues, "off-canter" cognition immediately following 3 days post-sports injury (competition or non-competition). Subjects were considered to have mild TBI if they were positive for three incidents.
RESULTS: The distribution of ADHD and mild TBI is noted in the table below:

		ADHD	
		yes	no
Mild TBI	yes	34	267
	no	5	144

There was a significant association between ADHD and mild TBI ($x2\ (1)= 7.94$. $p= 0.005$). Mild TBI occurred in 87.2% of the subjects with ADHD and at a lower rate of 65.0% in the

subjects without ADHD. ADHD was present in 11.3% of the subjects with mild TBI and at a lower rate of 3.4% in the subjects without mild TBI. Rates were similar in males and females. CONCLUSION: This examination revealed a significant association between ADHD and mild TBI in this sample of Egyptian competitive athletes. One caveat to these findings is the potential for selection bias as the subjects were being specifically queried for the presence of TBI. The association between ADHD and TBI we found is a similar finding to the results of the meta-analysis by Adeyemo et al.; however, as defined in the meta-analysis, it was not possible to determine the temporal association between ADHD and TBI in the current sample.

39. ADHD and Impairment in a North American Census-Based Sample

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Impairment ratings were obtained as part of the census-based normative standardization of the 3rd Revision of the Conners ADHD rating scale (Conners 3). Ratings were obtained from 1,568 parents, 1,746 teachers, and 1,371 self-reports of general population children and from a smaller sample of children diagnosed with ADHD. Results indicated that the ADHD sample was rated as being significantly more impaired than the general population sample in all three domains (School life, Relationships, Home life) with very large effect sizes (Cohen's *d* ranged from 1.24 to 4.80). Results also indicated the importance of collecting information from all three rater types (parents, teachers, self-report) across all three domains. Finally, for the ADHD group, a fair proportion of cases were rated as not having any impairment across the three domains which contradicts the DSM criterion that requires clinically significant impairment or decrease in functioning indicating that the assessment of impairment is required to help reduce over-diagnosis.

40. Psychometric Properties of the Conners Comprehensive Behavior Rating Scales

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The Conners Comprehensive Behavior Rating Scales (Conners CBRS) is an extended version of the Conners Rating Scales that provides comprehensive coverage of childhood disorders and concerns. It includes parent and teacher forms (for ages 6 to 18 years), and self-report forms (for ages 8 to 18 years). The parent, teacher, and self-report versions comprise 198, 204, and 181 items, respectively. The present report discusses the psychometric properties of the Conners CBRS in terms of its factor structure, reliability, and its ability to discriminate between diagnostic groups. The factor structure was highly consistent across the three versions and the factors were labeled Aggressive Behaviors, Emotional Distress, Academic Difficulties, Hyperactivity/Impulsivity, Separation Fears, Social Problems, and Perfectionistic/Compulsive behaviors. Reliability was high for the factor derived scales, as well as for all of the rationally derived scales, as evaluated through Cronbach's alpha and item-total correlations. Very large differences in terms of magnitude were observe between clinical cases and general population cases, supporting the ability of these new scales to differentiate between groups.

41. Psychometric Properties of the Conners 3rd Edition

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The Conners 3rd Edition (Conners 3), a revision of the Conners Rating Scales-Revised (CRS-R), is equipped with updated norms and item content focusing on Attention-Deficit Hyperactivity Disorder (ADHD) and its most co-morbid disorders and problems. The present report discusses the psychometric properties of the Conners 3. Specifically, the present report discusses the scale's stable factor structure, its strong levels of reliability and its ability to discriminate between various diagnostic groups. The Conners 3 will benefit potential users by serving as a statistically sound assessment of ADHD. Such an assessment will facilitate accurate identification of children with ADHD and can be used for intervention and treatment planning efforts.

42. Development of the Conners 3 ADHD Index

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The CRS-R, well validated measures of ADHD and other childhood psychopathology, included ADHD Indices that could be used as screening measures to identify youth likely to meet criteria for ADHD. With the revision of the CRS-R into the Conners 3rd Edition (Conners 3) updated ADHD Indices (Conners 3AI) have been created. The present study describes the development of these statistically sound Indices that can be used to distinguish youth with ADHD from those in the general population. The step-by-step development procedure is described, followed by a detailed analysis of the discriminative validity of the Conners 3AI. Results indicate that these forms can accurately distinguish youth with ADHD from those in the general population.

43. Development of the Conners Assessment System

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The Conners Rating Scales-Revised (CRS-R; Conners 1997) have been revised and expanded into the Conners Assessment System. The system includes two main tools: 1. The Conners 3rd Edition (Conners 3), a revision of the CRS-R that is specific to the assessment of ADHD its most common comorbid problems and disorders, and 2. The Conners Comprehensive Behavior Rating Scales (Conners CBRS) which is a new measure providing comprehensive coverage of childhood disorders and concerns. Both measures include parent and teacher forms (for ages 6 to 18 years), and self-report forms (for ages 8 to 18 years). The development of both measures began in 2004. Development goals and rationales were deter-mined by reviewing current theory, literature, and legislation, examining the strengths and weaknesses of similar instruments, and by holding several focus groups with clinicians and researchers. An initial item pool was developed and items were reviewed by an expert panel. A pilot study was conducted in order to assess the initial item statistics and factor structure of the forms, and items that failed to load onto a factor were eliminated or revised. In addition to the empirically derived factors, DSM symptom scales were developed on rational grounds. Three validity scales were also developed for both measures. Normative data were gathered and Factor Analyses were conducted from which the final factor structure of the assessments was finalized. All scales of the Conners 3 had

acceptable levels of internal consistency with Cronbach's alpha ranging from .84 to .97 for the content scales and from .78 to .95 for the DSM symptom scales. The Conners CBRS scales also demonstrated acceptable internal consistency with Cronbach's alpha ranging from .78 to .97 for the content scales, and from .73 to .94 for the DSM symptom scales. In 2014, the assessments were updated to include DSM-5 scoring.