ADHD & Substance Use Disorders

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Disclosures

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Some of the medications discussed may not be FDA approved in the manner in which they are discussed including diagnosis(es), combinations, age groups, dosing, or in context to other disorders (e.g. substance use disorders)
ADHD Overview

• Most common presenting neurobehavioral disorder in childhood
• Epidemiology: Worldwide 6-9% of children and adolescents; 4-5% of adults
• Chronic course characterized by inattention/distraction, impulsivity, and hyperactivity
• Associated with impairment in multiple domains
• Nonpharmacological and pharmacological treatments effective

(WiIens and Spencer, ADHD Across the Lifespan, Postgraduate Medicine: 2010; Faraone et al., Nature Neuroscience, 2015)
SUD is a Risk Factor for ADHD: Illustrative Overlap of ADHD in Adults With SUD

Overall, 23% of adults with substance abuse have ADHD (N=29 studies)*.

Childhood ADHD is Related to Future Cigarette and SUD

**Likelihood (Odds Ratio; OR) to Develop SUD**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biederman 2008</td>
<td>0.1864</td>
<td>0.2759</td>
<td>39.0%</td>
<td>1.20 [0.70, 2.07]</td>
<td>1.59 [1.12, 2.25]</td>
</tr>
<tr>
<td>Fischer 2002</td>
<td>0.5166</td>
<td>0.3019</td>
<td>32.9%</td>
<td>1.68 [0.93, 3.03]</td>
<td></td>
</tr>
<tr>
<td>Gittelman 1985</td>
<td>1.1367</td>
<td>0.4675</td>
<td>14.2%</td>
<td>3.12 [1.26, 7.78]</td>
<td></td>
</tr>
<tr>
<td>Mannuzza 1991</td>
<td>0.4261</td>
<td>0.4725</td>
<td>13.9%</td>
<td>1.53 [0.61, 3.87]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.59 [1.12, 2.25]</strong></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.01; Chi² = 3.12, df = 3 (P = 0.37); I² = 4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.60 (P = 0.009)</td>
<td></td>
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</tr>
</tbody>
</table>

**FIGURE 4** Meta-analysis of attention-deficit/hyperactivity disorder (ADHD) and psychoactive substance use disorder. Note: Results from a meta-analysis comparing ADHD versus control subjects for psychoactive substance use disorder. CI = confidence interval.

**Likelihood (Odds Ratio; OR) to develop Cigarette Smoking**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barkley 1990</td>
<td>0.8995</td>
<td>0.3301</td>
<td>25.0%</td>
<td>2.46 [1.29, 4.69]</td>
<td>2.36 [1.71, 3.27]</td>
</tr>
<tr>
<td>Biederman 2006</td>
<td>1.4019</td>
<td>0.4791</td>
<td>11.9%</td>
<td>4.06 [1.59, 10.39]</td>
<td></td>
</tr>
<tr>
<td>Elkins 2007</td>
<td>0.7514</td>
<td>0.2456</td>
<td>45.2%</td>
<td>2.12 [1.31, 3.43]</td>
<td></td>
</tr>
<tr>
<td>Milberger 1997</td>
<td>0.7207</td>
<td>0.3904</td>
<td>17.9%</td>
<td>2.06 [0.96, 4.42]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>2.36 [1.71, 3.27]</strong></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 1.62, df = 3 (P = 0.66); I² = 0%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.21 (P &lt; 0.00001)</td>
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</tr>
</tbody>
</table>

**FIGURE 6** Meta-analysis of attention-deficit/hyperactivity disorder (ADHD) and nicotine use. Note: Results from a meta-analysis comparing ADHD versus control subjects for nicotine use. CI = confidence interval.
A More Complicated Course of SUD Is Associated with ADHD

- More severe SUD
- Higher rates of other psychiatric comorbidities (e.g. conduct/antisocial disorders)
- Lower retention in SUD treatment
- Less remission from SUD
- Longer course of SUD

What Links ADHD and SUD?
ADHD Adults Do Not Selectively Abuse Specific Drugs

Classes of Drugs Abused in Adults With a Drug Use Disorder

ADHD and Control Adolescents are Similar in that Most Report Continuing to Use Substances for Self Medication

Adolescent impulsivity phenotypes characterized by distinct brain networks

Robert Whelan¹,², Patricia J Conrod³,⁴, Jean-Baptiste Poline⁵, Anbarasu LourduSamy³, Tobias Banaschewski⁶, Gareth J Barker³, Mark A Bellgrove⁶, Christian Büchel⁸, Mark Byrne², Tarrant D R Cummins², Mira Fauth-Bühler⁹, Herta Flor¹⁰, Jürgen Gallinat¹¹, Andreas Heinz¹¹, Bernd Ittermann¹², Karl Mann⁹, Jean-Luc Martinot¹³,¹⁴, Edmund C Lalor², Mark Lathrop¹⁵, Eva Loth³,¹⁶, Frauke Nees¹⁰, Tomas Paus¹⁷⁻¹⁹, Marcella Rietschel²⁰, Michael N Smolka²¹,²², Rainer Spanagel²³, David N Stephens²⁴, Maren Struve¹⁰, Benjamin Thyreau⁵, Sabine Vollstaedt-Klein⁹, Trevor W Robbins²⁵, Gunter Schumann³,¹⁶, Hugh Garavan¹,² & the IMAGEN Consortium²⁶

The impulsive behavior that is often characteristic of adolescence may reflect underlying neurodevelopmental processes. Moreover, impulsivity is a multi-dimensional construct, and it is plausible that distinct brain networks contribute to its different cognitive, clinical and behavioral aspects. As these networks have not yet been described, we identified distinct cortical and subcortical networks underlying successful inhibitions and inhibition failures in a large sample (n = 1,896) of 14-year-old adolescents. Different networks were associated with drug use (n = 1,593) and attention-deficit hyperactivity disorder symptoms (n = 342). Hypofunctioning of a specific orbitofrontal cortical network was associated with likelihood of initiating drug use in early adolescence. Right inferior frontal activity was related to the speed of the inhibition process (n = 826) and use of illegal substances and associated with genetic variation in a norepinephrine transporter gene (n = 819). Our results indicate that both neural endophenotypes and genetic variation give rise to the various manifestations of impulsive behavior.
Prevention of SUD in ADHD Youths
Treating Adolescents with OROS MPH Improves Smoking Outcomes (mean 10 mo [up to 24 mo]):

% current smoking according to Fagerstrom Tolerance Questionnaire

Non-ADHD (n=188)  OROS MPH (n=154)  ADHD Current Meds (n=46)  ADHD Not Current Meds (n=57)

8  7.1  10.9  19.6

p=0.01

Not significant (all p>0.20) * Not significant when controlled for CD, ETOH, drug abuse


- Periods of medication vs. non-medication within the same individual
  - In those ≤ age 15 at baseline
  - Each year of taking stimulant before FU
  - FU in 2009 (controlling for SES, psych disorder, and other confounders)
  - FU in 2009 (controlling for age, sex and meds)

Individuals were born 1960-1998 and diagnosed with ADHD (26,249 men and 12,504 women; circa 50% on stimulant medication in 2006);
Authors examined the association between stimulant ADHD medication in 2006 and substance abuse during 2009 (e.g. substance-related crime, hospital visits or death; outcomes ca 6% vs 0.5% ADHD vs gen pop)
Early and Longer Duration ADHD Treatment Reduces Past-Year Substance Use
(N=40,358: Monitoring the Future Survey, 10 Cohorts of senior years 2005 to 2014)

MTF U.S. Study: Early ADHD Treatment Reduces Marijuana Use in HS Seniors (N=40,358)

Population risk

- Stimulant use started prior to 9 years of age
- Stimulant use started between 10–14 years
- Stimulant use started after 15 years of age

Past Year Use

20%  30%  40%  50%  60%

10 Cohorts of high school seniors 2005 to 2014 (N = 40,358; ~10% with ADHD).
*P < .001 vs controls. Data depicts chronic exposure to stimulants (>6 years for 9, 10-14 yo; >3 years for 15+ yo)
Treatment Considerations in ADHD+SUD
SUD in ADHD Adults Presenting for Treatment

- SUD Current (10%)
- SUD History (40%)
- No SUD Hx (50%)

Diagnostic Dilemmas in ADHD + SUD

- Overlap symptoms of SUD in ADHD
  - Intoxication or withdrawal
  - Neuropsychological deficits (transient/permanent)
  - SUD “traits” misinterpreted as ADHD (e.g. impulsive traits/risk taking, harm avoidance)
- Other comorbidity (e.g. anxiety, disruptive disorders)
- Reliability of retrospective report
- Subthreshold ADHD vs full ADHD
  - Age-of-onset criteria (NOS)
  - Effected domains, inadequate number of symptoms
- Concerns of drug-seeking behavior/rationalization
- Use of ancillary information and/or rating scales for ADHD helpful (e.g ASRS)

For every complex problem, there is a simple solution

And it is wrong

George Bernard Shaw
Double-Blind Studies of Stimulants to Treat Current Substance Abusers with ADHD

6 Studies:
- 1 study in adolescent substance abusers administered Pemoline
- 2 studies in adult cocaine abusers administered IR or SR MPH
- 1 study in adult methadone maintenance patients administered SR MPH or SR-Bupropion
- 1 study in adults with briefly abstinent amphetamine abusers given OROS MPH
- 1 recent RCT -high dose Add XR showing improvement in ADHD/SUD

• Efficacy (vs placebo)
  - 5/6 no overall improvement in SUD (improvement in one)
  - Two studies suggest benefit in reducing ADHD symptoms on some measures but not others
  - One study showing improvement in ADHD and SUD (high dose AddXR)

• Safety
  - No serious adverse events
  - No worsening of SUD
  - No evidence of diversion

Higher Dose Mixed Amphetamine Salts XR in Helpful in ADHD & Cocaine Use Disorder (N=126)

13 week Randomized Controlled Trial
Diagnosis: Cocaine Use Disorder and ADHD
Treatment: CBT +/- MAS XR

Levin et al. JAMA Psychiatry. 2015;72(6):593-602
Atomoxetine Improves Outcome in Recently Abstinent Adults

An event ratio of 0.737 indicates that, relative to patients treated with placebo, atomoxetine-treated patients experienced an approximately 26.3% greater reduction in the rate of heavy drinking. Separation between groups first occurred at day 55.

Current Heavy Alcohol Use Worsens ADHD Symptoms
(AISRS Item Scores vs. Presence or Absence of Alcohol Abuse* in Placebo Group)

*AISRS = Adult ADHD Investigator Symptom Rating Scale; Appts = appointments; Conc. = concentration; NS = not statistically significant.

*Consumed ≥ 4 alcoholic drinks per day for women, or ≥ 5 drinks per day for men, within 24 hours (cumulative; drink = 1.5 oz. liquor, 5 oz. wine, 12 oz. beer), or ≥ 3 drinks/day for ≥ 1 week (i.e. ≥ 7 consecutive days), during the double-blind treatment period (visit 3–14 [BL to week 12]). P values were adjusted for multiple comparisons.
Methylphenidate for ADHD and Drug Relapse in Criminal Offenders with Substance Dependence: A 24-week Randomized Placebo-controlled Trial

Sample: 54 incarcerated males  
(Mean age 42 years)  
Dose: Start dose 18 mg  
MPH/placebo titrated over a period of 19 days to mean dose of 108 mg/day  
CBT: individual CBT once weekly for 12 weeks  
Measurements: Change in self-reported ADHD symptoms, urine tox, retention to treatment  
Findings: MPH treated group showed reduced ADHD symptoms (P = 0.011), significantly higher proportion negative urine screens (P = 0.047) and better retention (P = 0.032)

www.mghcme.org
The Complicated Relationship Between Attention Deficit/Hyperactivity Disorder and Substance Use Disorders

Courtney A. Zulauf 1, Susan E. Sprich 2, Steven A. Safren 3 and Timothy E. Wilens 1, 4, 5

Abstract

Adolescents and young adults with substance use disorders (SUD) and attention deficit/hyperactivity disorder (ADHD) are increasingly presenting in clinical practice. The overlap and role of treatment for these co-occurring conditions is not well understood. The purpose of the present review is to summarize recent literature on the treatment of adolescents and young adults with SUD and ADHD. The high risk for SUD in patients with ADHD and the high risk for ADHD in patients with SUD mandates the development of effective treatment strategies for each condition. Evidence from a recent Cochrane review indicates that treatment alone does not appear to be particularly effective in treating SUD in currently active substance abusing individuals with ADHD. Structured therapies may be effective in treating adolescents and young adults with ADHD and SUD. Further controlled trials evaluating the sequence and effect of structured psychotherapies and/or ADHD pharmacotherapy on SUD relapse in these groups are warranted.

Keywords  Adolescence – Substance use disorders – Attention deficit/hyperactivity disorder – Stimulants comorbidity – Cognitive-behavioral therapy

This article is part of the Topical Collection on Child and Adolescent Disorders

“...Structured therapies may be effective in treating adolescents and young adults with ADHD and SUD...”
Stimulant Misuse and Diversion

• N=22 Studies (N>113,000 participants); mostly survey studies in college students (80%)
• 10-20% prevalence of non medical use of stimulants
• 65-85% of stimulants diverted from “friends”
  – Majority not “scamming” local docs
  – Not seen as potentially dangerous
• Motivation typically for concentration/alertness > getting “high”
• Appears to be occurring in substance (ab)users during academic decline
• High rates of full or subthreshold stimulant use disorder in misusers
• High rates of ADHD and neuropsychological dysfunction in stimulant misusers
• More misuse of immediate vs extended release stimulant preparations

Conclusion

• ADHD is a risk factor for cigarette smoking and SUD

• ADHD should be considered in adolescents and adults who smoke cigarettes and/or have SUD

• Treating ADHD helps protect against the onset of cigarette smoking, SUD, and SUD-related criminality

• Treatment of ADHD+SUD should consider treatment of both conditions

• Stimulants have abuse liability-use extended release preparations in higher risk groups