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Towards Precision Addiction Treatment: New Findings in Co-morbid Substance Use and Attention-Deficit Hyperactivity Disorders

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Abstract Attention-deficit hyperactivity disorder (ADHD) and substance use disorders (SUDs) may have common etiologies. ADHD is more prevalent in patients with substance use disorders, and this pattern is consistent across different substances of abuse. Individuals with SUDs and ADHD exhibit significant variations in their clinical presentations. The developmental trajectory of ADHD to SUDs is complex: ADHD symptoms appear first in some patients but not in others. Many patients present with a heterogeneous collection of psychiatric and substance use co-morbidities, and these symptoms change over time. ADHD symptom severity is also highly variable, and more severe ADHD symptoms worsen co-morbid SUDs and complicate treatment. New longitudinal studies with innovative methods in high-risk populations and in community-based samples may clarify issues related to patient-treatment matching. When closely monitored, psychostimulant and other adjunct medications can be safely used to treat ADHD in this population, and such treatment may also improve outcome of SUDs. In particular, emerging evidence suggests individual-level tailoring ("precision medicine") approaches may represent a key pathway to improve clinical outcome.

Keywords Attention-deficit hyperactivity disorder · Substance use disorders · Comorbidity · Addiction · Stimulants · Cocaine · Clinical trials · Dopamine · Longitudinal study · Precision medicine

This article is part of the Topical Collection on *Substance Use and Related Disorders*

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Introduction

Attention-deficit hyperactivity disorder ADHD is a neurodevelopmental disorder with three symptom domains: (1) inattention: short attention span for age, difficulty listening, attending to interpersonal and sensory stimuli, and easy distractibility; (2) impulsivity: frequently interrupting others, having difficulty waiting for his or her turn, or risk-taking behavior; 3) hyperactivity: constant motion, excessive talking, and inability to stay on task. Recent evidence suggests persistent ADHD symptoms are associated with long-term negative outcomes such as educational failure and occupational impairment [1] and mortality [2••]. ADHD frequently co-occurs with other neuropsychiatric disorders. Matching patients with ADHD with appropriate treatment that address these co-morbidities represents an important public health challenge.

Co-morbid ADHD and Substance Use Disorders

In the past 20 years, numerous studies have provided evidence that ADHD is more prevalent in individuals with a substance use disorder. In early studies, the overall prevalence has varied between 10 and 15% in patients presenting with cocaine and alcohol users [3, 4] to 24% in a sample from chemical dependency treatment centers that also have a high co-morbid rate for conduct disorders [5]. In recent meta-analyses, the overall prevalence of ADHD in substance use disorder (SUD) patients was about 23.1% [6], with variations influenced by the diagnostic instrument and substance of abuse. Interestingly, cocaine was found to be associated with a lower ADHD prevalence. A large recent cross-sectional study showed that adult

ADHD prevalence in patients with SUDs varied between 5.4 and 31.3%, with an average of 14%, depending on the country, and prevalence estimates for DSM-5 (9–33%) were slightly higher than for DSM-IV [7•].

While early treatment studies have focused on co-morbid ADHD and cocaine use disorder, and in patients also with opioid use disorder [8], more recent studies indicate that a variety of substances of abuse, not limited to cocaine, are associated with ADHD symptoms [9]. The International ADHD in Substance Use Disorders Prevalence (IASP) study was the largest and newest epidemiological study in this area [10•] and reported that adjusting for other covariates, patients with ADHD had a higher prevalence of primary alcohol use disorder (34.5 vs. 8.2%, odds ratio 7.0) and other substance use disorders (29.0 vs. 16.7%, OR 3.4). More recently, increasing attention has been focusing on cannabis use disorder. In particular, adolescents who presented for cannabis use treatment also showed a high rate of ADHD [11], and similar patterns were observed in adults [12]. Given the higher prevalence of alcohol and cannabis use disorders, exploring ADHD in these patients represents a novel strategy for intervention.

Developmental Neuroscience: Common Pathways

Interest in characterizing ADHD as a developmental disorder has been motivated by the rise in SUDs in adolescents and the establishment of large cohort longitudinal studies such as *Monitoring the Future* in the 1970s [13]. Longitudinal studies of young children followed into adolescence and adulthood suggest overlapping symptoms of ADHD, such as difficulty with self-regulation, "novelty-seeking," fidgeting, and impulsive aggression, and identified a constellation of traits variously discussed as "behavioral undercontrol" [14] and "disinhibition" [15]. A consistent finding is that children with ADHD symptoms subsequently have a higher risk of developing an SUD, though evidence for specific substances of abuse, demographic features, and timing can be highly variable [16]. This led to the idea of a bidirectional casual process [17] of functional decline. Biological vulnerabilities predating substance use generate ADHD symptoms and related traits such as difficulty sustaining attention, impulsivity, and hyperactivity. These traits are related to neurocognitive deficits and executive dysfunction, which lead to childhood-onset impairments in academic and social domains. These impairments can then lead to conduct problems such defiance, rule breaking, and antisocial behavior. This triggers a higher risk for emergence and maintenance of SUDs, which in turn worsens functioning in adolescence and adulthood. SUDs more directly impair vocational and academic performance, as well as familial relationships, and these may present as stressors that worsen ADHD symptoms and other co-morbid psychiatric conditions, such as depression.

The discovery of effective pharmacological intervention for ADHD suggests both ADHD and SUD may represent abnormalities in related neural circuits and, in particular, circuits related to reward processing [18]. There is convincing evidence that ADHD is associated with underactivity of the dopamine reward pathway. Dopamine transporter (DAT) binding in positron emission tomography (PET) was diffusely decreased across different areas, including the nucleus accumbens (NAc), the midbrain, left caudate, and hypothalamus in patients with ADHD [19]. D2/3 receptor binding in the midbrain, caudate, and hypothalamus was shown to be significantly lower in patients with ADHD [20]. Similar deficits in dopamine activity were shown in patients with SUDs, including a blunted ventral striatal DA release after the administration of methylphenidate [21], and this deficit was associated with cue-induced craving [22]. Drug use increased dopamine release, and withdrawal induced a decrease in D2 receptors and dopamine release [20]. D2 reductions were associated with decreased activity in the anterior cingulate and orbitofrontal cortex and this may be a mechanism for compulsive drug administration [19]. The extent to which this effect occurs is variable, and some substance of abuse, such as cannabis and opiates, do not robustly increase dopamine levels [23]. Underactivity in these areas, part of the fronto-parietal executive function network, was also consistently associated with ADHD symptoms in demographically and clinically diverse samples [24], In summary, it appears that, overall, there is a deficit in dopamine transmission in both ADHD and SUDs, but the mechanism through which this deficit occurs, either with decreases in DAT/Dopamine receptors, or through decrease in dopamine binding and release, appears complex and heterogeneous.

A separate but related line of investigation in this area involves untangling the developmental neuroscience of delayed reward using primarily functional neuroimaging (fMRI). For example, there is some evidence that children with ADHD do not modify their behavior in the face of changing rewards [25], and similar deficits in delayed rewards existed in substance users [26]. fMRI data suggested decreased NAc activation for immediate and delayed rewards [27] and reward anticipation [28] in patients with ADHD. Furthermore, methylphenidate normalized differences in attention between children with ADHD and controls, and this effect is associated with upregulation of fronto-parietal executive function network and the temporal-parietal attentional network [29]. Several fMRI studies also suggested methylphenidate improved inhibitory control in the prefrontal cortex [30]. How and for whom dopamine release regulate these functional networks, and to what extent are these circuits modifiable through psychosocial interventions such as cognitive behavioral therapy (CBT), are active areas of investigation. A landmark large multi-site longitudinal study, Adolescent Brain Cognitive Development Study (ABCD), has been launched

recently to study the developmental trajectory of these functional circuits in the adolescent brain in time and their relations to the development of pathology. Results from this study will further shed light on the developmental neuroscience of ADHD and SUDs.

A focus of attention on development of co-morbid ADHD and SUDs recently turned to an interest cohort: individuals who meet all DSM-5 criteria for ADHD except the onset by age 12 [31]. Ninety percent of these individuals were de novo [32•], meaning they had neither met childhood criteria nor come close to meeting the full criteria in childhood. Childhood-onset ADHD patients exhibited significant neurocognitive symptoms, whereas adult-onset ADHD patients did not. Adult-onset ADHD patients showed a comparable or higher degree of SUDs and other psychiatric co-morbidities. Some, but not all, of these individuals may experience ADHD symptoms as a result of chronic substance use, especially dopamine-releasing drugs such as cocaine and amphetamine. These broad patterns of finding were replicated in two independent cohorts [33, 34], which showed that unlike childhood onset ADHD, "young-adult onset" ADHD was predominantly female [34], and these two groups were non-overlapping. Older and smaller neuroimaging studies, however, indicated that the structural features of the gray matter of these adult-onset ADHD patients (previously classified as ADHD not otherwise specified) were more similar to healthy controls rather than patients with childhood onset ADHD [35]. These findings may support the hypothesis that within the ADHD SUD co-morbid cohort, the age onset of ADHD presents a unique stratifying variable for targeted interventions to optimize functional improvement.

A few more additional patterns have emerged in the developmental trajectory in these individuals. First, psychopathology in addition to ADHD and SUDs is the rule rather than the exception. Common disorders include major depression, dysthymia, social phobia, and personality disorders [4, 14, 36]. In the new International ADHD and Substance Use Disorder Prevalence (IASP) dataset, 39.7% of individuals with primary alcohol use disorder and ADHD also have current depression, 34.5% of these patients have borderline personality disorder; 51.8% of all individuals with ADHD and any SUD have antisocial personality disorder [10]. Second, ADHD symptom subtypes are not stable longitudinally [37]: 52% of children with inattentive subtype and 33% of hyperactive subtype develop both symptom clusters (combined subtype) as adults; on the other hand, over 20% of children with combined subtype transition to either hyperactive or inattentive subtype in adults. Thirdly, the emergence of ADHD prior to SUDs are associated with a worse course of SUD, including earlier onset of SUDs, reduced probability, and longer time to remission, as well as poorer functional recovery [5, 14, 36].

Treatment: Towards Precision Addiction Medicine

Given the likely bidirectional causal relationship between symptoms of ADHD and SUDs throughout development, effective treatment of ADHD symptoms is a critical component in successful management of SUDs. However, there is ongoing concern with abuse and diversion of psychostimulants, the mainstays of pharmacotherapeutics of ADHD in patients with SUDs. From clinical experience, the abuse liability of prescribed psychostimulants, especially longer acting formulations, is low. Two studies from the National Drug Treatment Clinical Trials Network (CTN) evaluated subjective effects of osmotic-release oral systems methylphenidate (OROS-MPH) showed that adolescents with SUDs did not report euphoria more often, and not more likely to report losing pills or needing replacements between OROS-MPH and placebo [38], and no significant difference was detected in self-reported patterns of selling or misusing of medications. While IV cocaine and methylphenidate produce euphoria [21, 39], oral methylphenidate has a slower striatal uptake and, therefore, can effectively treat ADHD symptoms without producing significant euphoria.

A recent study examined nonmedical use and diversion of psychostimulants [40] showed a lower overall incidence (past year 1.1% for immediate-release amphetamine, 0.5% extended-release amphetamine, less than 0.5% for all methylphenidate formulations). Methylphenidate can be given safely to cocaine users without significantly affecting cardiovascular characteristics [41].

Psychostimulant treatment is a safe and effective treatment for ADHD symptoms, but is it also effective in curbing drug use in this co-morbid population? A recently meta-analysis of 13 outpatient pharmacologic trials [42] showed a mixed pattern: while ADHD symptoms improved, no overall beneficial effect on drug abstinence was detected. These studies have a variety of limitations, including high dropout rates, short time for outcome assessment, and under-dosing of stimulants and possible lack of patient-treatment matching. Two recent randomized controlled trials have shown promise in using robust dosing of psychostimulants in this population. First, a randomized controlled trial using OROS-MPH up to 180 mg daily in criminal offenders showed that those on MPH had greater retention in treatment, greater improvement in ADHD symptoms, and greater proportion of negative drug urine (23 vs. 16%) [43]. In another study with 126 outpatients at two centers, patients with both ADHD and cocaine use disorder who were treated with 80 mg of extended-release mixed amphetamine salt had a greater continuous abstinence

rates in the last 3 weeks compared to placebo (30 vs. 7%) when combined with CBT and voucher incentives for attendance [44•].

Two CTN studies testing methylphenidate for adolescent substance users [45] and adult smokers [46] demonstrate the importance of patient-treatment matching in this population. In both studies, methylphenidate did not show a significant effect overall for substance use outcomes. However, methylphenidate reduced substance use in adolescents with co-morbid conduct disorder [47]. In adults, methylphenidate improved nicotine abstinence in those with more severe ADHD but made it more difficult to achieve in individuals with less severe ADHD [48]. Computational modeling suggests optimal treatment assignment using a simple clinical rule, treating only patients with more severe cases with ADHD Rating Scale (ADHD-RS) >35 could further increase the rate of achieving prolonged abstinence from tobacco by 10% [49]. There are other potential pathways of treatment matching in this co-morbid population: early data suggest atomoxetine, a non-stimulant medication for ADHD, may be uniquely beneficial for alcohol use disorder [50] and this may be due to non-linear effects when combinations of drugs, such as alcohol and stimulants, are taken together [51]. These early treatment matching efforts are illustrations of a rapidly expanding area of research—"precision addiction medicine": the idea that the large number of possible treatment combinations for a complex, common, and heterogeneous condition such as ADHD with co-morbid SUD can be tailored and matched based on individual patient characteristics. For example, computational models may be constructed to estimate the risk for diversion and major side effects in prescription of psychostimulants for an individual patient and inform risk vs. benefit in clinical encounters; computer algorithms may suggest optimal pathways of psychopharmacology (stimulant vs. non-stimulant) based on a combination of data sources such as genetics, neuroimaging, and clinical characteristics; novel biomarkers that predict individual treatment response may be designed and tested based on our understanding of the common neural circuits involved in both ADHD and SUD.

Personalized and optimal treatment for ADHD and SUDs can have a large public health impact. Emerging evidence suggests that long-term treatment with medications may have a significantly positive public health impact, especially if treatment is targeted to high-risk groups. In a recently published naturalistic study, 60 male patients with severe SUDs and ADHD were followed after inpatient discharge for 1–2 years. The group that received ADHD medications had fewer substance relapses, more frequent voluntary treatments, and was more likely to be socially and vocationally rehabilitated [52]. A recent large registry-based study suggested that individuals with ADHD who received medications had a significant reduction in criminality compared to those who did not, with a potentially large effect size (relative risk reduction of 32% in men and 41% in women) [53]. At a systems level, precision medicine principles can be applied at a large scale: future research studies may examine whether individuals in treatment systems can be matched to different degree of resources in psychosocial interventions based on baseline characteristics; responses to treatment at an individual level may be tracked and interventions made adaptive in real time.

Conclusion

More than two decades of research has shown that ADHD and SUDs, seemingly distinct clinical syndromes, have common etiological origins, occur frequently together, contribute to the development and maintenance of each other, and may also benefit from common treatment strategies. Recently, focus on research has been dissecting the underlying neurobiological substrates, testing adequately dosed medications, patient-treatment matching, and large longitudinal pragmatic studies. A focus of current research effort involves predicting treatment response and tailoring intervention on an individual level. We are optimistic that this integrated approach for research in this area will yield important insights that will have significant public health consequences.

Compliance with Ethical Standards

Conflict of Interest Sean X. Luo serves as a consultant for Click Therapeutics, LLC.

Frances R. Levin reported receiving medication from USWorldMed for an ongoing study that is sponsored by the National Institute on Drug Abuse; serving as a consultant to GWPharmaceuticals and Eli Lilly and Co. from 2005 to 2007; serving on an advisory board to Shire in 2006 to 2007; and serving as a consultant to Major League Baseball regarding the diagnosis and treatment of attention-deficit/hyperactivity disorder.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Fredriksen M, Dahl AA, Martinsen EW, Klungsoyr O, Faraone SV, Peleikis DE. Childhood and persistent ADHD symptoms associated with educational failure and long-term occupational disability in adult ADHD. Atten Defic Hyperact Disord. 2014;6:87–99.
2.•• Dalsgaard S, Ostergaard SD, Leckman JF, Mortensen PB, Pedersen MG. Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. Lancet. 2015;385:2190–6. **This study showed that ADHD is associated with increased mortality in individuals with ADHD in a large longitudinal cohort**.
3. Clure C, Brady KT, Saladin ME, Johnson D, Waid R, Rittenbury M. Attention-deficit/hyperactivity disorder and substance use:

symptom pattern and drug choice. Am J Drug Alcohol Abuse. 1999;25:441–8.
4. Levin FR, Evans SM, Kleber HD. Prevalence of adult attention-deficit hyperactivity disorder among cocaine abusers seeking treatment. Drug Alcohol Depend. 1998;52:15–25.
5. Schubiner H, Tzelepis A, Milberger S, Lockhart N, Kruger M, Kelley BJ, et al. Prevalence of attention-deficit/hyperactivity disorder and conduct disorder among substance abusers. J Clin Psychiatry. 2000;61:244–51.
6. van Emmerik-van Oortmerssen K, Crunelle CL, Carpentier PJ. Substance use disorders and ADHD: an overview of recent Dutch research. Tijdschr Psychiatr. 2013;55:861–6.
7.• van de Glind G, Konstenius M, Koeter MW, van Emmerik-van Oortmerssen K, Carpentier PJ, Kaye S, et al. Variability in the prevalence of adult ADHD in treatment seeking substance use disorder patients: results from an international multi-center study exploring DSM-IV and DSM-5 criteria. Drug Alcohol Depend. 2014;134:158–66. **Early results in variability of ADHD prevalence in a cross-cultural epidemiological study**.
8. King VL, Brooner RK, Kidorf MS, Stoller KB, Mirsky AF. Attention deficit hyperactivity disorder and treatment outcome in opioid abusers entering treatment. J Nerv Ment Dis. 1999;187:487–95.
9. van Emmerik-van Oortmerssen K, van de Glind G, van den Brink W, Smit F, Crunelle CL, Swets M, et al. Prevalence of attention-deficit hyperactivity disorder in substance use disorder patients: a meta-analysis and meta-regression analysis. Drug Alcohol Depend. 2012;122:11–9.
10.• van Emmerik-van Oortmerssen K, van de Glind G, Koeter MW, Allsop S, Auriacombe M, Barta C, et al. Psychiatric comorbidity in treatment-seeking substance use disorder patients with and without attention deficit hyperactivity disorder: results of the IASP study. Addiction. 2014;109:262–72. **Most recent large epidemiological study for the prevalence of ADHD and co-morbidities in different populations**.
11. Zaman T, Malowney M, Knight J, Boyd JW. Co-occurrence of substance-related and other mental health disorders among adolescent cannabis users. J Addict Med. 2015;9:317–21.
12. Notzon DP, Pavlicova M, Glass A, Mariani JJ, Mahony AL, Brooks DJ, Levin FR. ADHD is highly prevalent in patients seeking treatment for cannabis use disorders. J Atten Disord. 2016.
13. Johnston LD, O'malley PM, Bachman JG, Schulenberg JE. Monitoring the future national survey results on drug use, 1975–2010. Volume II, College Students & Adults Ages 19-50. Institute for Social Research. 2011.
14. King KM, Chassin L. Mediating and moderated effects of adolescent behavioral under control and parenting in the prediction of drug use disorders in emerging adulthood. Psychol Addict Behav. 2004;18:239–49.
15. Iacono WG, Malone SM, McGue M. Behavioral disinhibition and the development of early-onset addiction: common and specific influences. Annu Rev Clin Psychol. 2008;4:325–48.
16. Molina BS, Pelham Jr WE. Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. J Abnorm Psychol. 2003;112:497–507.
17. Molina BS, Pelham Jr WE. Attention-deficit/hyperactivity disorder and risk of substance use disorder: developmental considerations, potential pathways, and opportunities for research. Annu Rev Clin Psychol. 2014;10:607–39.
18. Lee SS, Humphreys KL, Flory K, Liu R, Glass K. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. Clin Psychol Rev. 2011;31:328–41.
19. Volkow ND, Fowler JS, Wang GJ, Goldstein RZ. Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. Neurobiol Learn Mem. 2002;78:610–24.
20. Volkow ND, Wang GJ, Kollins SH, Wigal TL, Newcorn JH, Telang F, et al. Evaluating dopamine reward pathway in ADHD: clinical implications. JAMA. 2009;302:1084–91.
21. Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Jayne M, et al. Profound decreases in dopamine release in striatum in detoxified alcoholics: possible orbitofrontal involvement. J Neurosci. 2007;27:12700–6.
22. Wong DF, Kuwabara H, Schretlen DJ, Bonson KR, Zhou Y, Nandi A, et al. Increased occupancy of dopamine receptors in human striatum during cue-elicited cocaine craving. Neuropsychopharmacology. 2006;31:2716–27.
23. Nutt DJ, Lingford-Hughes A, Erritzoe D, Stokes PR. The dopamine theory of addiction: 40 years of highs and lows. Nat Rev Neurosci. 2015;16:305–12.
24. Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP, et al. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. Am J Psychiatry. 2012;169:1038–55.
25. Kollins SH, Newland MC, Critchfield TS. Human sensitivity to reinforcement in operant choice: how much do consequences matter? Psychon Bull Rev. 1997;4:208–20.
26. Heil SH, Johnson MW, Higgins ST, Bickel WK. Delay discounting in currently using and currently abstinent cocaine-dependent outpatients and non-drug-using matched controls. Addict Behav. 2006;31:1290–4.
27. Plichta MM, Vasic N, Wolf RC, Lesch KP, Brummer D, Jacob C, et al. Neural hyporesponsiveness and hyperresponsiveness during immediate and delayed reward processing in adult attention-deficit/hyperactivity disorder. Biol Psychiatry. 2009;65:7–14.
28. Strohle A, Stoy M, Wrase J, Schwarzer S, Schlagenhauf F, Huss M, et al. Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder. Neuroimage. 2008;39:966–72.
29. Rubia K, Halari R, Cubillo A, Smith AB, Mohammad AM, Brammer M, et al. Methylphenidate normalizes fronto-striatal underactivation during interference inhibition in medication-naive boys with attention-deficit hyperactivity disorder. Neuropsychopharmacology. 2011;36:1575–86.
30. Konova AB, Moeller SJ, Tomasi D, Volkow ND, Goldstein RZ. Effects of methylphenidate on resting-state functional connectivity of the mesocorticolimbic dopamine pathways in cocaine addiction. JAMA Psychiat. 2013;70:857–68.
31. Castellanos FX. Is adult-onset ADHD a distinct entity? Am J Psychiatry. 2015;172:929–31.
32.• Moffitt TE, Houts R, Asherson P, Belsky DW, Corcoran DL, Hammerle M, et al. Is adult ADHD a childhood-onset neurodevelopmental disorder? Evidence from a four-decade longitudinal cohort study. Am J Psychiatry. 2015;172:967–77. **This is the recent study showing that adult onset ADHD may be a distinct clinical entity**.
33. Agnew-Blais JC, Polanczyk GV, Danese A, Wertz J, Moffitt TE, Arseneault L. Evaluation of the persistence, remission, and emergence of attention-deficit/hyperactivity disorder in young adulthood. JAMA Psychiat. 2016;73:713–20.
34. Caye A, Rocha TB, Anselmi L, Murray J, Menezes AM, Barros FC, et al. Attention-deficit/hyperactivity disorder trajectories from childhood to young adulthood: evidence from a birth cohort supporting a late-onset syndrome. JAMA Psychiat. 2016;73:705–12.
35. Proal E, Reiss PT, Klein RG, Mannuzza S, Gotimer K, Ramos-Olazagasti MA, et al. Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood. Arch Gen Psychiatry. 2011;68:1122–34.
36. Wilens TE, Kwon A, Tanguay S, Chase R, Moore H, Faraone SV, et al. Characteristics of adults with attention deficit hyperactivity disorder plus substance use disorder: the role of psychiatric comorbidity. Am J Addict. 2005;14:319–27.

37. Kaye S, Ramos-Quiroga JA, van de Glind G, Levin FR, Faraone SV, Allsop S, Degenhardt L, Moggi F, Barta C, Konstenius M, Franck J, Skutle A, Bu ET, Koeter MW, Demetrovics Z, Kapitany-Foveny M, Schoevers RA, van Emmerik-van Oortmerssen K, Carpentier PJ, Dom G, Verspreet S, Crunelle CL, Young JT, Carruthers S, Cassar J, Fatseas M, Auriacombe M, Johnson B, Dunn M, Slobodin O, van den Brink W. Persistence and subtype stability of adhd among substance use disorder treatment seekers. J Atten Disord. 2016.
38. Winhusen TM, Lewis DF, Riggs PD, Davies RD, Adler LA, Sonne S, et al. Subjective effects, misuse, and adverse effects of osmotic-release methylphenidate treatment in adolescent substance abusers with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2011;21:455–63.
39. Volkow ND, Chang L, Wang GJ, Fowler JS, Franceschi D, Sedler M, et al. Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. J Neurosci. 2001;21:9414–8.
40. Cassidy TA, Varughese S, Russo L, Budman SH, Eaton TA, Butler SF. Nonmedical use and diversion of ADHD stimulants among U.S. adults Ages 18–49: a national internet survey. J Atten Disord. 2015;19:630–40.
41. Collins SL, Levin FR, Foltin RW, Kleber HD, Evans SM. Response to cocaine, alone and in combination with methylphenidate, in cocaine abusers with ADHD. Drug Alcohol Depend. 2006;82:158–67.
42. Cunill R, Castells X, Tobias A, Capella D. Pharmacological treatment of attention deficit hyperactivity disorder with co-morbid drug dependence. J Psychopharmacol. 2015;29:15–23.
43. Konstenius M, Jayaram-Lindstrom N, Guterstam J, Beck O, Philips B, Franck J. Methylphenidate for attention deficit hyperactivity disorder and drug relapse in criminal offenders with substance dependence: a 24-week randomized placebo-controlled trial. Addiction. 2014;109:440–9.
44.• Levin FR, Mariani JJ, Specker S, Mooney M, Mahony A, Brooks DJ, et al. Extended-release mixed amphetamine salts vs placebo for comorbid adult attention-deficit/hyperactivity disorder and cocaine use disorder: a randomized clinical trial. JAMA Psychiat. 2015;72:593–602. **A two-site study showing a robust dose of psychostimulant may be effective in treating both SUD and ADHD simultaneously**.
45. Riggs PD, Winhusen T, Davies RD, Leimberger JD, Mikulich-Gilbertson S, Klein C, et al. Randomized controlled trial of osmotic-release methylphenidate with cognitive-behavioral therapy in adolescents with attention-deficit/hyperactivity disorder and substance use disorders. J Am Acad Child Adolesc Psychiatry. 2011;50:903–14.
46. Winhusen TM, Somoza EC, Brigham GS, Liu DS, Green CA, Covey LS, et al. Impact of attention-deficit/hyperactivity disorder (ADHD) treatment on smoking cessation intervention in ADHD smokers: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2010;71:1680–8.
47. Tamm L, Trello-Rishel K, Riggs P, Nakonezny PA, Acosta M, Bailey G, et al. Predictors of treatment response in adolescents with comorbid substance use disorder and attention-deficit/hyperactivity disorder. J Subst Abuse Treat. 2013;44:224–30.
48. Nunes EV, Covey LS, Brigham G, Hu MC, Levin FR, Somoza EC, et al. Treating nicotine dependence by targeting attention-deficit/hyperactivity disorder (ADHD) with OROS methylphenidate: the role of baseline ADHD severity and treatment response. J Clin Psychiatry. 2013;74:983–90.
49. Luo SX, Covey LS, Hu MC, Levin FR, Nunes EV, Winhusen TM. Toward personalized smoking-cessation treatment: using a predictive modeling approach to guide decisions regarding stimulant medication treatment of attention-deficit/hyperactivity disorder (ADHD) in smokers. Am J Addict. 2015;24:348–56.
50. Wilens TE, Adler LA, Weiss MD, Michelson D, Ramsey JL, Moore RJ, et al. Atomoxetine ASUDSG. Atomoxetine treatment of adults with ADHD and comorbid alcohol use disorders. Drug Alcohol Depend. 2008;96:145–54.
51. Kirkpatrick MG, Gunderson EW, Levin FR, Foltin RW, Hart CL. Acute and residual interactive effects of repeated administrations of oral methamphetamine and alcohol in humans. Psychopharmacology (Berl). 2012;219:191–204.
52. Bihlar Muld B, Jokinen J, Bolte S, Hirvikoski T. Long-term outcomes of pharmacologically treated versus non-treated adults with ADHD and substance use disorder: a naturalistic study. J Subst Abuse Treat. 2015;51:82–90.
53. Lichtenstein P, Halldner L, Zetterqvist J, Sjolander A, Serlachius E, Fazel S, et al. Medication for attention deficit-hyperactivity disorder and criminality. N Engl J Med. 2012;367:2006–14.