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Pharmacological Treatment of ADHD in Addicted Patients: What Does the Literature Tell Us?

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Abstract

Learning objectives—After participating in this activity, learners should be better able to:

- Evaluate pharmacologic treatment of attention deficit/hyperactivity disorder (ADHD) in patients with substance use disorder (SUD)
- Assess the causes of the diminished efficacy of ADHD medication in patients with comorbid SUD

Objective—Substance use disorder (SUD) and attention-deficit/hyperactivity disorder (ADHD) frequently co-occur, and the presence of ADHD complicates the treatment of the addiction.

Pharmacotherapy is a potent intervention in childhood and adult ADHD, but findings have been mixed in adolescent and adult ADHD patients with SUDs. This review focuses on several contributing factors and possible explanations, with implications both for future research and for clinical practice.

Method—This systematic review examined all randomized, placebo-controlled trials of pharmacotherapy for ADHD in adult and adolescent SUD patients.

Results—The number of studies is limited, and several studies are hampered by qualitative flaws. The results, in general, are inconclusive for most medications studied, but more recent trials using psychostimulants in robust dosing have demonstrated significantly positive results.

Conclusion—In reviewing these trials, possible explanations relating to the particular characteristics and problems of this complex patient group are discussed. Several factors, including ADHD symptom severity, psychiatric comorbidity, persistent drug use, choice of medication, and concomitant psychosocial intervention, influence study results. Taking these factors into account may improve the likelihood of detecting significant effects in future research, as the recent positive trials have indicated, and may help in the appropriate selection of pharmacotherapy in clinical practice.

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The manuscript discusses the use of ADHD medication (amphetamine, atomoxetine, bupropion, and methylphenidate) in ADHD adults with substance use disorders. The Food and Drug Administration has not specifically approved the use of these medications for such purposes.

Keywords

adult; ADHD; atomoxetine; comorbidity; dexamphetamine; methylphenidate; pharmacotherapy; placebo; randomized controlled trial; substance use disorder

INTRODUCTION

The past decades have seen an increased awareness of the relevance of attention-deficit/hyperactivity disorder (ADHD) in the development and persistence of problematic substance use. An increased prevalence of ADHD (mean = 23.1%; 95% confidence interval [CI], 19.4%–27.2%) has systematically been found in various groups of patients with different substance use disorders (SUDs).¹ Further, studies have shown not only that ADHD plays a role in the origin and the development of addictive behavior but also that the presence of untreated ADHD negatively influences SUD treatment outcomes.^{2–4} These findings have led to substantial efforts to improve treatment of ADHD in these patient groups.⁵ ADHD has been shown to be eminently treatable with pharmacotherapy in children and adults without psychiatric comorbidities.^{6–8}

The rationale for using ADHD medication in patients with comorbid ADHD and SUD is primarily twofold: to improve ADHD symptomatology and to positively influence addiction outcome.^{9,10} Effective treatment would stabilize cumbersome ADHD symptoms, making patients more stable and more amenable to treatment. Moreover, it could help them to remain abstinent, by improving their cognitive control and by reducing their impulsivity and restlessness. A possible additional reason to use ADHD medication in the presence of comorbid ADHD and SUD is as a substitution therapy in stimulant dependence. A specific problem, however, concerns the abuse liability of stimulant medication, making ADHD medication a less straightforward choice for ADHD patients with SUDs.¹¹

The excellent results in adult ADHD, with 40% to 75% of patients responding positively to medication,^{7,12} have not been matched in patients with comorbid SUDs,^{13,14} as will be discussed in more detail later. Case reports and open studies have reported marked success of medication on ADHD and even SUD parameters.^{15–20} Randomized trials, however, have long struggled to show a marked efficacy of pharmacotherapy for ADHD or a positive influence of ADHD treatment on the course of the addiction.^{13,21} Variability in medications and dosing regimens, as well as low retention in treatment, may have contributed to these negative results.

As advances in treatment for ADHD in SUD remain a relevant topic, our goal in writing this review was to synthesize these conflicting findings. The studies under review here are quite varied in patient population and medication selection, thus making direct comparison difficult. We will therefore discuss each study separately before identifying more general patterns.

In addition, we will discuss several hypotheses for the lack of efficacy of medication. As several lines of research suggest that amelioration in ADHD symptoms may increase the

likelihood of reducing substance use and reaching abstinence, we will indicate key issues for the improvement of pharmacotherapy, both for research and for clinical practice.

METHODS

A MEDLINE/PubMed search was conducted to identify randomized, placebo-controlled trials that examined the efficacy of pharmacological treatment for adolescent and adult patients with ADHD and comorbid SUD (the last search was performed on 20 July 2015). Initial elimination of articles was done through title and abstract by the first author: only double-blind, placebo-controlled trials were considered in the review. Articles that did not include ADHD and SUD diagnoses as inclusion criteria or that did not report on comorbid treatment efficacy were eliminated. As the studies were quite heterogeneous, published over an extended timeframe (2002–15), and required the use of differing keywords, it was difficult (even retrospectively) to retrieve all studies using only MEDLINE/PubMed searches. The reference lists of retrieved studies and relevant review articles (e.g., Faraone et al. [2004], Koesters et al. [2009], Perez de los Cobos et al. [2012], Cunill et al. [2015]) were examined to identify any further studies.^{13,21–23} Using the criteria indicated, 14 articles were retained for the current review.

REVIEW OF RANDOMIZED, CONTROLLED TRIALS OF PHARMACOLOGICAL TREATMENT FOR ADHD IN SUD

The relevant studies are limited in number but heterogeneous in several aspects. Nearly all studies aimed to study the efficacy of ADHD medication both on ADHD symptomatology and SUD outcome parameters. The great variety in patient populations, types of SUD, treatment settings, study medications, and outcome measures preclude any direct comparison. We therefore decided to briefly present each study, grouping the studies according to the medications used; this classification is not entirely satisfactory, as only one drug (methylphenidate) was extensively studied. Next, we list the main study characteristics and outcomes in two summary tables, detailing the outcome measures and instruments used, allowing for a more technical comparison.

Improvement on differing ADHD symptom-rating scores was the primary ADHD outcome measure, next to clinical improvement rating (Clinical Global Impression); functional improvement never figured as an outcome measure. For SUD, both subjective (number of abstinent days, duration of abstinence) and objective measures (urine screens) were used.

Methylphenidate: 8 Studies

Schubiner (2002)—This first study on the subject, with 48 currently cocaine-abusing participants, used classic short-acting methylphenidate (up to 30 mg three times a day).²⁴ The results showed a significant difference favoring active treatment on clinician-rated and patient-rated efficacy indices, but no significant difference in the ADHD Symptom Checklist score or in substance use measures. Both groups received cognitive-behavioral therapy (CBT) to help them cope with their ADHD symptoms, especially as they related to their substance use disorder.

Carpentier (2005)—The first European study is the only one in an inpatient setting; all 25 participants were in inpatient treatment for their various addictions.²⁵ As abstinence was controlled for by the clinical setting, the trial was primarily focused on ADHD symptomatology. Because of this design (multiple crossover: A-B-A-B), the study would have been sufficiently powered to detect any clinically significant effect of active treatment (methylphenidate IR [immediate-release], 15 mg three times daily) on ADHD symptomatology, even with this small number of participants. The study failed to show any difference, however, between active treatment and placebo. This result was attributed to a combination of a strong placebo response, the probable influence of the inpatient setting, and the use of a suboptimal dose of methylphenidate.

Levin (2006)—This study, the only one in opioid-addicted patients, involved methadone-maintenance therapy in 98 participants randomly assigned to one of three treatment arms: methylphenidate (sustained-release [SR], 20–40 mg twice daily), bupropion SR (400 mg), and placebo.²⁶ A reduction in ADHD symptoms (the primary outcome measure) was observed in all three groups, but no significant difference between treatments was found, nor any influence of treatment on substance use. The placebo response in ADHD symptomatology was high. The lack of effect of active treatment was partially attributed to the continued use of substances other than methadone (cocaine, cannabis, alcohol), the high psychiatric comorbidity of this patient group,²⁷ the concomitant CBT, and the use of a methylphenidate formulation with less reliable bioavailability.²⁸

Levin (2007)—This trial administered methylphenidate (SR, up to 60 mg/day) or placebo in cocaine-addicted participants. No difference between groups was found on the primary outcome measures of ADHD symptomatology and substance use.²⁹ Again, both groups improved on ADHD symptomatology, but drug use remained largely unchanged. Some secondary measures, assessing the association between ADHD response and substance use, favored active treatment. Specifically, for the methylphenidate group, ADHD treatment responders, compared to nonresponders, were more likely to have a reduction in cocaine use. The lack of overall therapeutic effect was partially ascribed to the use of inadequate doses of a possibly less efficacious formulation, the same problem as in the study immediately above.^{26,28}

Konstenius (2010)—The first published trial using OROS (osmotic-controlled release oral-delivery system) methylphenidate (fixed dose of 72mg/day) failed to be superior to placebo.³⁰ Both groups in this small study of 24 amphetamine-addicted participants reported a reduction in their self-reported ADHD symptoms, again with no difference between groups. No difference in drug use or craving was observed. The lack of significant effect here was due to the small sample size, substantial dropout rate (though in line with the other studies), and fixed medication dosage.

Riggs (2011)—This study was by far the largest and most ambitious, with 303 adolescent participants with at least one non-tobacco SUD (mostly alcohol, cannabis, and cocaine). It was sufficiently well powered to detect a difference between active treatment (OROS methylphenidate, titrating up to a single dose of 72 mg daily) and placebo,³¹ with both

groups receiving CBT. Compliance was high, and the study medication was well tolerated. Both groups showed significant improvement in ADHD symptomatology and substance use at the end of the 16-week trial. Disappointingly, no statistically significant difference was found between the two groups on primary outcome measures (e.g., self-reported drug/alcohol use). Some secondary measures (parent ADHD-rating scale, problem-solving score, number of negative urine samples) favored active treatment, though in both groups (whether methylphenidate or placebo), participants who responded to treatment had a significantly higher number of negative urine screens. CBT had a surprisingly strong positive effect on ADHD and was seen as a major factor in the inability to differentiate between the two groups. When parental reporting was used as an ADHD outcome measure, however, the improvement in the active group was significantly better, suggesting that parents' report might be the preferable outcome measure.

Further analysis revealed interesting predictive value of patient characteristics on pharmacotherapy outcomes.³² For both groups, more severe substance use was associated with poorer ADHD and SUD outcomes, and more severe ADHD symptomatology was associated with better ADHD and SUD outcomes. The presence of conduct disorder (CD) decreased the likelihood of ADHD improvement, though CD participants showed greater improvement on SUD measures with methylphenidate compared to placebo.

Konstenius (2014)—The key characteristics in this latest methylphenidate study were the use of a modern formulation (OROS methylphenidate) in substantially higher dosages (up to 180 mg/day) and for the extended study period of 24 weeks.³³ The treatment population was atypical: 54 amphetamine-addicted men, recruited during prison incarceration. Medication was started 2 weeks prior to release and then continued in outpatient care. Despite the high dropout rate, the results were clear and unequivocal: active treatment improved ADHD symptomatology and retention in treatment. The active-treatment group had a greater proportion of amphetamine-negative urines. Rates of continuous abstinence were not provided. Unlike earlier studies, patients were abstinent when they were placed on medication.

Winhusen (2010)—This study is somewhat different as it concerns ADHD adults with nicotine dependence only, specifically without other substance disorders. Nicotine dependence is common in ADHD adults, but its influence has not been systematically evaluated in the other trials. OROS methylphenidate (up to 72 mg) was compared to placebo both on ADHD symptoms and on smoking cessation.³⁴ To help the participants quit smoking, they received nicotine-replacement therapy (by way of a transdermal patch) and individual counseling. With a large sample size of 255 participants, a good retention rate, and high compliance, active treatment was markedly superior to placebo in improving ADHD symptoms—a result similar to previous methylphenidate trials in ADHD adults without SUDs. Active treatment had no significant effect, however, in promoting nicotine abstinence.

Given that psychostimulants are the first-choice medication in adult ADHD,³⁵ it is not surprising that one of them, methylphenidate, has been the most extensively studied drug in this patient population. In striking contrast to several studies in ADHD adults without SUDs,

which have found robust standard mean differences in outcome measures (reported from 0.58 to 0.74),^{36,37} the results in ADHD adults with SUDs are inconclusive, with only the latest trial showing significant positive results.³³

Amphetamine: 2 Studies

Levin (2015)—The most recently published study also used a stimulant in dosages higher than usually prescribed. It is the first using amphetamine (sustained-release mixed amphetamine salts), comparing two robust dosages (60 and 80 mg/day) in a population of ADHD patients with cocaine addiction.³⁸ The results of this sufficiently powered study (with good treatment retention) are notable: active treatment not only significantly reduced ADHD symptomatology but also improved SUD outcome measures (with better abstinence in the highest-dosage group, consistent with other agonist-replacement strategies).

Kollins (2014)—This pilot study is the first using the promising amphetamine compound lisdexamfetamine (in dosages up to 70 mg/day), here as an adjunct to nicotine-replacement therapy in adult smokers wanting to quit.³⁹ It is a small study, both in scale (32 participants) and in time (four weeks of active treatment vs. placebo). ADHD symptoms significantly improved with active treatment, but no differences in smoking outcomes were found between groups, as both groups significantly reduced smoking.

In spite of its long tradition as an effective medication in ADHD children and adults, amphetamine has not been systematically studied until recently in ADHD patients with SUDs. The results shown here are promising and merit further study. The potential of lisdexamfetamine in this patient group is still largely unexplored. Whether amphetamine is more suitable than methylphenidate for ADHD and SUD patients remains to be settled.

Atomoxetine: 3 Studies

Wilens (2008)—The first study on atomoxetine (up to 100 mg) in adults targeted only alcohol dependence, focusing on very recently abstinent ADHD adults at high relapse risk to heavy alcohol use.⁴⁰ Results showed that atomoxetine had a significant positive effect on ADHD symptomatology but no effect on the primary measure of alcohol use: time to relapse to heavy drinking (timeline follow-back method). A secondary outcome measure (the number of heavy drinking days) indicated some positive effect of active treatment on the addiction, as it showed a reduction by 26% in the atomoxetine-treated participants.

Thurstone (2010)—The first study with atomoxetine (up to 100 mg) in adolescents with various SUDs (mainly alcohol and cannabis, equally distributed between the two treatment groups) failed to demonstrate a significant effect of active treatment: both active-treatment and placebo groups showed similar improvement on ADHD symptomatology or substance use.⁴¹ This result was ascribed to the concurrent use of motivational interviewing and CBT, and to a high placebo response.

McRae-Clark (2010)—In this small study, atomoxetine (up to 100 mg/day) was used in 38 marijuana-dependent participants.⁴² Since this trial was characterized by a substantial dropout rate, a study-completer analysis was used. Improvement on some but not all ADHD

symptom measures was found in the active-treatment group. No group difference was found in cannabis use, the trial's primary outcome measure.

Overall, atomoxetine has a favorable track record in adult ADHD, with positive response rates up to 44%,^{43,44} and is often presented as a more suitable drug for ADHD patients with SUDs because of its once-daily dosage and lack of abuse potential. The number of studies in this specific population is limited, however, and its efficacy for ADHD remains to be demonstrated convincingly.

Bupropion: 1 Study

Levin (2006)—As indicated above, the only study in opioid-addicted patients in methadone maintenance therapy also used bupropion as one of three treatment arms; methylphenidate (SR 20–40 mg twice daily), bupropion SR (400 mg), and placebo.²⁶ In this single study (with a particular group of participants), bupropion failed to show a significant effect.

Pemoline: 1 Study

Riggs (2004)—The first study conducted in ADHD adolescents with various SUDs used pemoline (75–112.5 mg), an atypical stimulant, later withdrawn from the market because of a risk of liver damage.⁴⁵ The results showed a significant reduction on the parent-rated ADHD scale in pemoline-treated study completers but no difference in the primary outcome using an intent-to-treat analysis. Substance use did not decline in either group.

GENERAL COMPARISON

The following tables summarize the studies presented here. Table 1 lists the main study features, including type of addiction, number of participants, medication used, and main effect on ADHD and SUD outcomes. For a relative estimation of the effect, the ADHD and SUD outcome measures were compared, as summarized in Table 2. In the absence of a “gold standard” outcome measure, different instruments, with differing characteristics, were used. Also, studies differed in their choice of a primary outcome measures. In our comparison, effect sizes were estimated not only on the statistical significance of the results but also on the discriminative quality of the relevant outcome measure. For ADHD, a significant change in mean ADHD symptomatology score is easier to achieve than a significant change in a more demanding categorical outcome, such as a 30% reduction in symptom score. For SUD, a significant difference in the proportion of negative urines or days of abstinence is a less demanding treatment target than a significant difference in the duration of continuous abstinence. In this way, a study with a significant difference on a more discriminative primary outcome measure is graded ++. A positive effect on a secondary outcome measure allows for a + grade (Table 1). In grading the studies, we also considered other factors influencing the quality of the study and the relevance of the findings (study population size, retention rate, medication formulation, and dosage).

We appreciate the limitations of this imprecise effect comparison. Nevertheless, our conclusions are similar to other reviews that have analyzed the same studies in greater detail;^{13,21–23} a limitation of meta-analytical approaches is that they may overlook other issues influencing the quality and results of the different studies. In our opinion our

approach is an appropriate way to bring out the main conclusion of our review—namely, that ADHD pharmacotherapy, given at standard doses, has diminished efficacy in SUD patients.

IDENTIFYING MORE GENERAL TRENDS

In contrast to the robust positive outcomes recorded in studies in ADHD adults without addiction and without comorbidities, the results of the studies in addicted ADHD patients have been disappointing though not entirely negative. Not surprisingly in this study population, most studies suffer from low retention rates (Table 1), which further complicates the interpretation of the results in study completers. With the exception of two studies,^{24,25} the studies reviewed here used an intention-to-treat analysis. Two studies used a modified intention-to-treat approach^{40,42} and included only the participants with at least one post-randomization assessment.

A further problem in interpreting these results is the wide diversity in these studies, not only in patient characteristics and choice of medication, but (especially) in outcome measures.

The results of several studies fell into a similar pattern: ADHD symptoms tended to improve in both active-treatment and placebo groups, with active treatment struggling to show a significant difference. Most of the studies, however, suggested some benefit of active treatment (secondary outcome measures) on ADHD symptoms and even in terms of substance use, particularly if ADHD responded to active treatment. This trend is clearly visible in the two most recent studies.^{33,38}

REVIEW OF POSSIBLE EXPLANATIONS OF DIMINISHED MEDICATION EFFICACY

Several reasons in combination, and as considered below, probably account for the diminished efficacy of ADHD medication in SUD patients.

Incorrect ADHD Diagnosis

Unreliable diagnostic assessment of ADHD can lead to incorrect diagnoses and thereby contribute to unclear trial results. ADHD is a more challenging diagnosis in a population of SUD patients, as ADHD symptoms can be disguised or mimicked by the influence of substance use (or withdrawal). Moreover, it is unclear whether chronic substance use can induce concentration problems and inhibitory dyscontrol, or can aggravate previously existing ADHD symptoms. Confirmation of a lifelong history of ADHD symptoms by multiple sources can be more difficult because of strained family relations. Chances of an incorrect diagnosis are reduced (but not eliminated) by using standardized diagnostic instruments,⁴⁶ which was the case in most studies reviewed.

Participant Characteristics

An indication of an ethnic influence in treatment response has been found in a secondary analysis of the OROS methylphenidate trial in smokers,⁴⁷ revealing that nonwhite participants had significantly higher rates of abstinence than white participants and also that they perceived a greater reduction in desire to smoke and withdrawal symptoms while on

active medication. A clear explanation is lacking, which illustrates how specific, but mostly unknown, participant characteristics may significantly influence outcome.

Is ADHD Different in SUD Adults?

An unanswered question is whether the combination of ADHD and SUD is an expression of a distinct (and more severe) subtype of ADHD, less responsive to standard pharmacotherapy. As this question concerns the relationship between ADHD and addiction, a definite answer will come only with better knowledge of the relevant genetic and other etiological factors, as well as the pathogenetic mechanisms, involved in both disorders.

ADHD Severity

Another secondary analysis of the OROS methylphenidate trial in smokers showed that patients with more severe ADHD at baseline (particularly individuals with an ADHD rating score greater than 35) and also those with more improvement of their ADHD symptoms while on active treatment had higher rates of prolonged abstinence.^{48,49} As mentioned, a similar finding was found in a further analysis of the methylphenidate trial in adolescents, where more severe ADHD was associated with better ADHD and SUD out-comes.³² Interestingly, the methylphenidate trial in cocaine-dependent patients already showed that participants with a positive response on active treatment had a higher proportion of cocaine-negative urine samples.²⁹

An alluringly logical explanation can be found for these results: not only do SUD patients with more severe ADHD have a larger room for improvement regarding their ADHD symptomatology and resulting dysfunction, but their addiction has the greater potential to benefit from this improvement as well. In pharmacotherapy trials in adult ADHD patients, symptom severity has also been found to be a predictor of positive treatment response.^{50,51} If more severe ADHD is a significant driving factor in addiction, then significant improvement in ADHD symptoms may improve the likelihood of successful addiction treatment.

The Influence of Psychiatric Comorbidity

A distinct feature of ADHD in SUD patients is the high prevalence of comorbid psychiatric disorders. Several studies have documented higher rates of psychiatric comorbidity, especially mood and anxiety disorders, but also conduct disorder and personality disorders, in subjects with SUD and ADHD relative to subjects with SUD, ADHD, or controls.^{27,52,53} Typically, the best results of pharmacotherapy in ADHD have been obtained in adults without psychiatric comorbidities.^{37,54,55} Both past and present comorbid disorders can influence the efficacy of medication in direct (e.g., probable influence on neurobiological processes) and indirect (e.g., diminished therapeutic compliance) ways.

Of special note, a history of conduct disorder is quite common in this patient group.^{56–58} The question has been raised whether the combination of ADHD and CD is a distinct subtype.^{59,60} Antecedents of CD have not been systematically evaluated in the majority of the trials; the presence of CD in the large adolescent study reduced the probability of a positive ADHD treatment effect of active treatment.³² Substance use was more likely to be reduced

among, however, ADHD participants with CD who received methylphenidate compared to placebo. How a CD history negatively affects the response of ADHD, but not of substance use, to ADHD pharmacotherapy remains unclear. The assumption is that efficacy for ADHD is negatively influenced by the additional burden of psychiatric comorbidity and the conduct disturbances associated with CD but that the burden may be less for substance use.^{61,62}

The Type of Substance Use

A related question concerns the impact that each type of addiction may have on study results. In most studies, participants were addicted to various substances, showing mixed results. In the single study executed in this patient group, ADHD in opioid-dependent patients proved particularly difficult to treat.²⁶ It is unclear whether that was due to the specific characteristics of opioid dependence or to the multiple problems (both comorbid psychopathology and psychosocial problems) of these complex patients.^{27,63}

With atomoxetine, better results were obtained in alcohol-dependent patients⁴⁰ than in those with cannabis and other SUDs.^{41,42} One study on the genetic transmission in families found genetic linkage between ADHD and drug dependence, whereas ADHD and alcohol dependence were found to behave as two independent disorders.⁶⁴ This finding is consistent with considering the combination of ADHD and SUD to be a specific subtype of adult ADHD, and offers some clues for the different results of ADHD pharmacotherapy in drug-dependent versus alcohol-dependent patients.

Interestingly, the presence of nicotine dependence does not seem to influence methylphenidate efficacy.^{34,39}

The Influence of Previous Drug Use

Neurobiological studies have consistently shown that prolonged exposure to psychoactive drugs leads to neuroadaptive changes in several brain circuits, further enhancing addictive behavior.^{65–67} Repeated drug administration triggers neuroplastic changes in glutamatergic inputs to the striatum and midbrain dopamine neurons, enhancing the brain's reactivity to drug cues, reducing the sensitivity to nondrug rewards, weakening self-regulation, and increasing dysphoria and the sensitivity to stressful stimuli.⁶⁸ The exact influence of these changes on ADHD pathophysiology is unknown, but it seems plausible that long-term use of these psychoactive substances, by interacting with and influencing the same neurotransmitter systems, will negatively influence the efficacy of ADHD medication; the impact of past substance use is the main reason why some ADHD patients with past addictions may need dosages higher than usual to achieve full efficacy.

The Influence of Persistent Drug Use

By the same token, persisting use of psychoactive substances will reduce efficacy even more, not only at the neurobiological level described above, but also by diminishing therapeutic compliance while under the influence of drugs. This could be a major explanation for the disappointing results of several trials, as they were done in an outpatient setting; participants were not abstinent at baseline (Table 1); and for most participants, abstinence proved hard to achieve or maintain. It should be noted, too, that the pattern of

rapid improvement early in the course of several trials would suggest that the severity of some ADHD symptomatology could be substance induced and could be improving because of early abstinence. Taken together, these considerations suggest that ensuring abstinence may improve the detection of a medication effect in pharmacotherapeutic trials.

Influence of Medication Selection and Formulation

Only two drugs have been studied in at least two trials: methylphenidate (eight studies) and atomoxetine (three studies). Given its documented efficacy in adult ADHD, methylphenidate was an obvious choice; on the face of the results discussed above, it is unclear whether methylphenidate should remain a first option for this patient group. However, additional factors seem to be involved. The first studies have been executed with older formulations, both immediate release^{24,25} and sustained release;^{26,29} the therapeutic effect of these formulations is less reliable and therapeutic compliance is more problematic.

Suboptimal dosing is probably another factor,²⁵ as there is mainly anecdotal evidence of ADHD patients needing dosages higher than standard (>1 mg/kg/day) to achieve symptom remission. The hypothesis is that SUD patients are more likely to have a dysregulation of brain dopamine neurotransmission, due to adaptation from chronic psychoactive drug use.^{68,69} This hypothesis is supported by the positive results of the latest methylphenidate and amphetamine trials using higher than standard dosages.³³

The therapeutic potential of the second major psychostimulant, amphetamine, has been insufficiently explored, as the positive results of a recent trial indicate.³⁸ In line with the comment above, these positive results were also obtained with robust dosages. This option has become even more interesting, as a prodrug with diminished abuse potential, lisdexamfetamine, is now available.⁷⁰

As discussed, the atomoxetine trials showed mixed results. Atomoxetine has also been used in an open trial in cocaine-dependent patients;⁷¹ in spite of improvement on ADHD symptomatology, the trial was marked by a high dropout rate and a lack of influence on cocaine use.

Placebo Effect

In several studies ADHD symptomatology tended to decrease in both active-treatment and placebo groups.^{25,29,31,41} Some level of placebo effect seems to be involved.²⁵ In most ADHD pharmacotherapy trials in children and adults (without addiction), a more discrete placebo effect has been observed, with a positive response in 10%–30% of participants. This placebo effect in ADHD treatment is clearly less important than in other psychiatric disorders, such as depression and anxiety disorders, with positive responses in up to 50% of participants. When active therapy has only a limited effect, however, even a moderate placebo effect makes it harder to establish a significant positive effect of active treatment.

The expectations of participants have been shown to influence study results.⁷² This mechanism could be another explanation for the pattern of early improvement seen in several studies. An unanswered question is whether patient selection plays a role here, as some trials would potentially attract more motivated volunteers.

Influence of Concurrent Treatment

In several studies the concurrent treatment of the SUDs seems to have contributed to the decrease of ADHD symptomatology in both active-treatment and placebo groups. This effect was most obvious in the large study in adolescents,³¹ but the other studies have shown a similar trend. In assisting the development of effective compensatory strategies, CBT can help to decrease the functional impairments of ADHD. By focusing on organizing and planning, managing avoidance, and decreasing dysfunctional thoughts and cognitions, CBT has been shown to be effective for adult ADHD.^{73–75} The use of similar methods and strategies in the CBT for SUD could explain why CBT (or a similar psychosocial interventions), embedded in the structure of a therapeutic trial, could positively affect ADHD symptomatology and dysfunction. As any psychosocial treatment would require some time to have a therapeutic effect, the benefit of concurrent CBT would be seen somewhat late in the trial.

Although CBT may thus benefit participants, it possibly interferes with the detection of a treatment effect. The improvement makes it harder for active treatment to demonstrate an additional positive impact except when the response to active treatment is itself robust. Interestingly, in the trials in this review, the concurrent psychosocial treatment (mostly focused on SUDs) had a larger influence on ADHD symptomatology than on addiction outcomes. This finding remains to be investigated in detail; it could be that ADHD patients, in particular, benefit (short-term) from the structuring influence of the intervention. An interesting hypothesis is that a positive effect of CBT in SUD would require high cognitive processing; if so, the implication is that in this specific population, SUD improvement by means of CBT would be achieved only after the ADHD is sufficiently stabilized.

Summary

This array of confounding factors puts a new perspective on the trial results, which become more useful than they appeared at first glance. While most trials came up with inconclusive results, they still offer valuable lessons in optimizing pharmacotherapy in this complex patient group—namely, by taking into account all the variables that have been discussed in this section.

The failure to obtain positive results required researchers to look for possible explanations and to try to design future trials to address these issues. A wide variety of factors (e.g., ADHD severity, patient characteristics, type of addiction, type and dose of medication, and study design) contribute to the final outcome. The conclusion may well be that pharmacotherapy for ADHD in addicted patients is feasible and effective, but not for all patients in all circumstances. Identifying limiting factors prior to treatment can help to mitigate their influence.

The valuable lessons learned from these studies may help us to optimize the chances of effective ADHD treatment. Not only do these past studies have important consequences for future research, but they also offer valuable advice for clinical practice. These will be discussed in the following sections.

DISCUSSION

Consequences for Future Research

Several of the hypotheses formulated in the previous section provide an invitation for further fundamental neurobiological research on the pathophysiology of SUD in ADHD patients and the differing effects of medication. In the meantime, in order to increase the chances for a positive effect (and to better understand the causes of a lack of it), future randomized pharmacotherapy trials in this patient population should take several factors into account.

Patient selection and assessment—Only patients with a clear ADHD diagnosis should be included in randomized trials. Despite the difficulties mentioned above, ADHD can be reliably diagnosed in SUD patients using standardized diagnostic instruments.

ADHD severity—The assessment should include an instrument for measuring ADHD symptom severity before and during the trial; clinical indications suggest that chances of a positive effect (both on ADHD and on substance use) increase with increasing symptom severity.^{32,48} To maximize this effect, only patients with more severe ADHD symptomatology (i.e., a high ADHD symptomatology cutoff score, with clear and disturbing symptoms) should be selected for participation.

Comorbidity assessment—In view of the prevalent comorbidity, a detailed psychiatric assessment should be part of the diagnostic evaluation. The type and severity of the SUD should be described. Antecedents of conduct disorder should be systematically checked; a dimensional score of CD symptoms has been informative in earlier research.⁷⁶ This kind of extensive psychiatric assessment should be accompanied by genetic sampling, which would provide valuable material for future studies (eventually leading to a retrospective genetic confirmation of the prior diagnosis).

Abstinence monitoring and control—Pharmacotherapy should be tested in abstinent patients. As this will be difficult to maintain in an outpatient setting, systematic monitoring of abstinence should be performed, preferably by objective measures (such as urine screens). A preparatory phase before starting pharmacotherapy may be helpful in this regard. Focusing on abstinence imposes additional requirements, as participants may need a behavioral/psychosocial platform to support their abstinence attempt. This same intervention can help to maintain treatment retention.

Medication selection—The importance of earlier experiences has been borne out in the latest methylphenidate trial,³³ in which positive results were achieved using a modern sustained-release formulation in higher dosages. It will be interesting to see whether these results can be replicated in similar conditions. Meanwhile, since methylphenidate will not be effective for all patients, alternatives need to be studied. The first alternatives are long-acting amphetamine formulations. Their potential has been demonstrated in the recently published trial with sustained-release mixed amphetamine salts, using a similar strategy of robust dosing.³⁸ Because therapy adherence is a specific problem in this patient population, long-acting formulations are strongly preferred.

Control for placebo effect—Study planning should take the possible placebo effect into account, both in the power calculation and in the study design. One possibility is to use a placebo lead-in for all treatment groups, which would enable one to remove those with low motivation and a high placebo-response rate prior to randomization and, in addition, would provide baseline data that incorporate expectancy effects. Selecting patients with more severe symptomatology also offers a greater buffer for a concomitant placebo effect.

Describe concurrent treatment—Often, concurrent psychotherapy is provided in pharmacotherapy trials in SUDs to enhance medication adherence or retention in treatment. As discussed above, concurrent therapy may be a necessary requirement if participants are asked to remain abstinent during the trial. Given the possible impact that various psychotherapies might have on ADHD and substance use, the type and intensity of therapy need to be described and preferably to be provided in a standardized way, so that its influence on the results can be studied effectively.

Standardize outcome measures—A consistent way of measuring ADHD and SUD improvement has been lacking; outcome measures have been similar but not identical, hindering direct comparison and generalization of results. The field would benefit from more uniform and consistent outcome measures. Studies should aim for robust improvement occurring across various measures—not only in isolated outcome parameters.

For ADHD outcomes, self-reports are insufficient and should be supplemented by observer reports. Improvement in a categorical measure (e.g., a 30% reduction in symptomatology score) can be clinically more relevant than a statistically significant reduction in mean symptomatology score. For SUD outcomes, self-reports should be substantiated by urine screens. Prolonged abstinence may be a more clinically meaningful outcome measure than an increase in negative urine screens or individual days of abstinence.

Alternatives for randomized, controlled trials?—This review describes the efficacy of ADHD pharmacotherapy in addicted patients in randomized, controlled trials. While this design is feasible, all of the contributing factors cannot be adequately addressed. One way to address this problem might be to use naturalistic studies. These offer the possibility of trying different medications, following a guideline or a specified treatment algorithm. This kind of standardized clinical experience would offer valuable information on the respective merits of different medications, preferably matched to detailed patient characteristics.

Consequences for Clinical Practice

As previously described, numerous issues make it challenging to treat ADHD in SUD patients. Although the available evidence is not sufficient to draw firm conclusions, the experience gained from the reviewed studies is valuable for clinical practice. The main implications are discussed below.

More research is required to develop clear guidelines for ADHD pharmacotherapy in SUD patients. Meanwhile, medication can potentially contribute to the multimodal treatment of these dual-diagnosis patients. Efficacy of pharmacological treatment may be improved if limiting and facilitating factors are identified and if treatment conditions are optimized. Not

all patients will benefit equally. Identifying the causes of diminished efficacy may be a valuable first step in overcoming poor treatment response.

In view of complications discussed above, the clinician might consider selecting patients with a better chance of a positive result: well-motivated patients with clear and severe ADHD symptomatology who are willing to abide to the conditions of treatment and to try and remain abstinent. This does not mean that treatment should be withheld for less suitable candidates. Rather, they should be informed about the possibilities and limitations of pharmacotherapy, and advised how to increase their chances of success. Since the best results will be achieved in a reliable therapeutic alliance, strengthening the patient's motivation and commitment can be a worthwhile investment.

The starting point is a clear ADHD diagnosis based on a reliable procedure, preferably with information from multiple sources (partner, friends, family). A thorough psychiatric assessment will provide a clear picture of other psychiatric, somatic, and psychosocial problems that may influence prognosis. In the case of complex patients with multiple comorbid psychiatric disorders, a clear treatment plan should indicate which disorders and problems should be addressed first. In most of these cases, although ADHD treatment would not have the highest priority, early stabilization of ADHD symptomatology (by means of pharmacological treatment) would likely improve the treatability of the other disorders.

As indicated, a standardized instrument for measuring ADHD symptom severity will be useful; the patients likely to benefit most from treatment are those identified as having more-severe symptomatology.

Patients should be well informed about the possible effects of medication and the importance of abstinence during the trial period. In principle, medication is not started when substance use is insufficiently under control. The commitment to abstinence can be used to monitor commitment to therapy. Urine screens can be valuable in this respect; patients should be reassured that the screens are not being used punitively but to enable them to objectively demonstrate their commitment to achieving abstinence. Further, a discussion about the importance of abstinence during the trial period can facilitate, in turn, a discussion of how best to achieve that goal. Patients can be informed that successful pharmacological treatment of ADHD may help them to remain abstinent.

When abstinence is deemed critical or proven unattainable in an outpatient setting, a brief inpatient stay may be used for detoxification and for initiation of medication treatment. While abstinence may be preferable, as demonstrated by the recent study conducted in amphetamine-dependent released prisoners, the combination of effective medication and CBT was able to facilitate abstinence in ADHD adults with cocaine dependence.³⁸

The available evidence precludes the recommendation of specific drugs. Pharmacotherapy in ADHD patients with SUDs will obviously be not as effective as in patients without SUDs, but it is still worthwhile to utilize standard ADHD medications.²¹ It is therefore necessary to discuss available options from the start. Some of the newer preparations are not available in all countries, or patients cannot afford them. Medications should be tried for a sufficiently long time (at least four weeks for stimulants, at least six weeks for other medications such as

atomoxetine and bupropion) and in adequate dosages.⁷⁷ The clinical situation will heavily influence the choice of medication.

In suitable patients, psychostimulant medication still remains the first choice; of note, in none of the studies reviewed was psychostimulant treatment associated with an increase in substance use. The newer, long-acting preparations are clearly to be preferred, both for improving adherence and for minimizing the risk of diversion and abuse. Lisdexamfetamine (a prodrug, consisting of dexamphetamine and the amino acid lysine) offers similar advantages, but the drug has not yet been systematically evaluated in this patient group.⁷⁰ As discussed, higher dosages than usual (methylphenidate: up to 2 mg/kg/day, and if necessary, even higher) can be tried, depending on the level of positive response and side effects. Close monitoring of dosage and effect is essential and is not feasible without a good working relationship with the patient. Moreover, patients need to be selected carefully since stimulant medications can produce cardiovascular and psychiatric adverse effects. The same holds true for dextroamphetamine (doses up to 1 mg/kg/day). Short-acting formulations for both methylphenidate and dextroamphetamine can still be used, but with clear restrictions—not only because of abuse liability but also because of adherence problems. Again, patient commitment is essential to achieve significant results.

Atomoxetine should be considered in patients with greater risk of medication abuse. Although it is frequently recommended in SUD patients because of its lack of abuse potential, empirical (as discussed) and clinical evidence of its efficacy is not yet convincing. Consequently, except when the likelihood of abuse is substantial, and perhaps among those with alcohol use disorder, it is not a first-choice medication for this overall patient group.

Next in line is bupropion, although it is not approved by the Food and Drug Administration for treating ADHD. For other medications, evidence is even more deficient. In any event, a sound principle is to continue medication only if there is a convincingly positive effect (which is also one of the best guarantees for continued patient adherence).

The combination of ADHD and SUDs is a complex constellation, in most cases complicated by further psychopathology and psychosocial problems. To improve the chances of making a valuable contribution to treatment, pharmacotherapy should be part of an integrated treatment program, tackling both ADHD and addiction as well as additional comorbid disorders and psychosocial issues. The treatment of these additional problems may improve therapy and medication adherence.

CONCLUSION

In spite of mixed research results, the future for ADHD pharmacotherapy in SUD patients is not bleak. Caveats notwithstanding, the evidence suggests that ADHD and comorbid SUDs may be treated with good effect. Modern psychostimulant formulations, which improve patient adherence and reduce the risk of diversion and abuse, have become increasingly available. There is still room for improvement, and both the scientific literature and increasing clinical experience have provided valuable indications how to move forward. The aim is not only to stabilize ADHD symptoms but also to reduce substance use and promote

abstinence. As more recent trials have demonstrated, with improved attention to confounding and facilitating factors, pharmacotherapy may be effective in treating ADHD patients with comorbid substance use disorders, helping them to overcome their addiction.

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Double-Blind, Placebo-Controlled, Randomized Trials of ADHD Medication in Adolescent^a and Adult SUD Patients

Table 1

Study	Sample size	Medication and maximum dose	SUD type	Duration (weeks)	Abstinence at baseline	Completers (%)	Concurrent therapy	Effect on ADHD ^b	Effect on SUD ^b	Remarks
Schubiner et al. (2002) ²⁴	48	Methylphenidate IR 3 × 30 mg	Cocaine	12	No	Active: 45% Placebo: 58%	Group CBT	+	0	
Carpentier et al. (2005) ²⁵	25	Methylphenidate IR 3 × 15 mg	Various ^c	8	Yes	Active/ placebo: 76%	Inpatient treatment	0	Not evaluated	ADHD improvement in both treatment groups
Levin et al. (2006) ²⁶	98	Methylphenidate SR 2 × 20–40 mg Bupropion 400 mg	Opioid	12	No	Active: 66/70% Placebo: 76%	CBT	0	0	Methodone-maintained patients 3-arm design
Levin et al. (2007) ²⁹	106	Methylphenidate SR 40 + 20 mg	Cocaine	14	No	Active 43% Placebo: 45%	CBT	0	0(+)	ADHD improvement in both treatment groups
Konstenius et al. (2010) ³⁰	24	Methylphenidate (OROS) 72 mg	Amphetamine	12	Yes	Active: 59% Placebo: 84%	Skills training	0	0	Fixed-dose methylphenidate
Winhusen et al. (2010) ³⁴	255	Methylphenidate (OROS) 72 mg	Nicotine	11	No	Active: 81% Placebo: 79%	Nicotine patch Counseling	++	0	
<i>Riggs et al. (2011)³¹</i>	<i>303</i>	<i>Methylphenidate (OROS) 72 mg</i>	<i>Various^c</i>	<i>16</i>	<i>No</i>	<i>Active: 78% Placebo: 72%</i>	<i>CBT</i>	<i>0(+)</i>	<i>0(+)</i>	<i>ADHD improvement in both treatment groups</i>
Konstenius et al. (2014) ³³	54	Methylphenidate (OROS) 180 mg	Amphetamine	24	Yes	Active: 30% Placebo: 7%	CBT	+	+	
Levin et al. (2015) ³⁸	126	Amphetamine (MAS) 60 or 80 mg	Cocaine	13	No	Active: 75/79% Placebo: 67%	CBT	++	++	
Kollins et al. (2014) ³⁹	32	Lisdexamfetamine 70 mg	Nicotine	4	Yes	Active: 82% Placebo: 93%	Nicotine patch Counseling	++	0	Smoking reduction in both treatment groups
Wilens et al. (2008) ⁴⁰	147	Atomoxetine 25–100 mg	Alcohol	12	Yes	Active: 44% Placebo: 64%	12-steps participation only	++	0(+)	Improvement on measures of alcohol use
<i>Thurstone et al.(2010)⁴¹</i>	<i>70</i>	<i>Atomoxetine 25–100 mg</i>	<i>Various^c</i>	<i>12</i>	<i>No</i>	<i>Active: 91% Placebo: 94%</i>	<i>MI/CBT</i>	<i>0</i>	<i>0</i>	<i>ADHD improvement in both treatment groups</i>
McRae-Clark et al. (2010) ⁴²	38	Atomoxetine 100 mg	Marijuana	12	No	Active: 32% Placebo: 38%	MI	+	0	
<i>Riggs et al. (2004)⁴⁵</i>	<i>69</i>	<i>Pemolide 75–112.5 mg</i>	<i>Various^c</i>	<i>12</i>	<i>No</i>	<i>Active: 54% Placebo: 50%</i>	<i>none</i>	+	<i>0</i>	<i>No differences in intent-to-treat analysis</i>

^aItalics denote studies of adolescents.

^bThe following symbols indicate effectiveness: 0 = no significant difference; +/+/+/++ = strength of the difference (with a positive effect of active treatment); () = effectiveness in secondary analysis.

^cSUD types in study populations with various addictions (in order of decreasing frequency):

Carpentier et al. (2005);²⁵ cocaine, alcohol, cannabis

Riggs et al. (2011);³¹ cannabis, alcohol, cocaine

Thurstone et al. (2010);⁴¹ cannabis, nicotine, alcohol

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Riggs et al. (2004).⁴⁵ cannabis, nicotine, alcohol

CBT, cognitive-behavioral therapy; IR, immediate-release formulation; MAS, mixed amphetamine salts; ML, motivational interviewing; MMT, methadone maintenance treatment; OROS, osmotic-controlled release oral-delivery system; SR, sustained-release formulation (duration of action: 4–6 hours); SUD, substance use disorder.

Primary Outcome Measures and ADHD and SUD Instruments Used in the Randomized Trials of ADHD Medication in Adolescent^a and Adult SUD Patients

Table 2

Study	Medication	SUD type	Primary outcome measure (if indicated) and quality ^b	ADHD outcome measure and effect ^c	SUD outcome measure and effect ^c
Schubiner et al. (2002) ²⁴	Methylphenidate	Cocaine	(ADHD: +) (SUD: +)	ADHD symptom checklist, physician rated: ++ ADHD symptom checklist, self-rated +	Urine screens: 0 Tiffany Cocaine Craving Scale: 0 Self-report: 0
Carpentier et al. (2005) ²⁵	Methylphenidate	Various ^d	(ADHD: +)	ADHD Rating Scale-IV (Dupaul): 0 Clinical Observation Scale (Barkley): 0 CGI: 0	
Levin et al. (2006) ²⁶	Methylphenidate Bupropion	Opioid (MMT)	ADHD WRAADDS 30% reduction: ++	WRAADDS: 0 CGI: 0	Self-report: 0 Urine screens: 0
Levin et al. (2007) ²⁹	Methylphenidate	Cocaine	ADHD AARS 30% reduction: ++ SUD No, positive cocaine weeks: ++ No, participants achieving abstinence: ++	AARS: 0 CGI: 0 Targeted Adult ADD Scale (Wender): 0	Self-report: 0 Urine screens: 0 (+)
Konstenius et al. (2010) ³⁰	Methylphenidate (OROS)	Amphetamine	(ADHD: +) (SUD: +)	CAARS-SV: 0 CAARS-O: 0	Self-report (TLFB): 0 Tiffany Cocaine Craving Scale: 0 Urine screens: 0
Winhusen et al. (2010) ³⁴	Methylphenidate (OROS)	Nicotine	SUD Prolonged abstinence: ++	ADHD-RS: ++ CGI: ++	Self-report (TLFB): 0
Riggs et al. (2011) ³¹	Methylphenidate (OROS)	Various	ADHD ADHD-RS: + SUD No. days of drug use (TLFB): +	ADHD-RS (adolescent informant): 0 ADHD-RS (parent informant): ++ CGI: 0	Self-report (TLFB): 0 Urine screens: +
Konstenius et al. (2014) ³³	Methylphenidate (OROS)	Amphetamine	(ADHD-RS: +) (ADHD CGI: ++)	CAARS-SV: ++ CGI: 0 Retention in treatment: ++	Urine screens: ++ Craving for Amphetamine Scale: +
Levin et al. (2015) ³⁸	Amphetamine MAS	Cocaine	ADHD No, 30% reduction on AISRS: ++ SUD No, cocaine-abstinent weeks (urine screens + self-report): ++	AISRS: ++ CAARS-O: ++ CGI: ++	Self-report (TLFB): ++ Urine screens: ++
Kollins et al. (2014) ³⁹	Lisdexamfetamine	Nicotine	SUD Prolonged abstinence: ++	CAARS-SV: ++	Self-report (N cigarettes/day): 0
Wilens et al. (2008) ⁴⁰	Atomoxetine	Alcohol	ADHD AISRS: + SUD TLFB: +	AISRS: ++ Adult ADHD Self-Report Scale: + CGI: +	TLFB: 0 (+) Obsessive Compulsive Drinking Scale: +
Thurstone et al. (2010) ⁴¹	Atomoxetine	Various	ADHD ADHD symptom checklist: + SUD Self-report: +	ADHD symptom checklist-I: 0 ADHD symptom checklist parent: 0 CGI: 0	Self-report (TLFB): 0 Urine screens: 0
McRae-Clark et al. (2010) ⁴²	Atomoxetine	Marijuana	SUD Self-report: +	WRAADDS: 0 CGI: +	Self-report: 0 Drug screens: 0 CGI: 0

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Study	Medication	SUD type	Primary outcome measure (if indicated) and quality ^b	ADHD outcome measure and effect ^c	SUD outcome measure and effect ^c
<i>Riggs et al. (2004)^{d5}</i>	<i>Pemolide</i>	<i>Various</i>	<i>ADHD CGI-I +; Conners' HI Scale: + SUD Interview +; urine screens: +</i>	<i>CGI: ++ Conners' HI Scale: 0</i>	<i>Follow-up interview (TLFB): 0 Urine screens (treatment effectiveness score): 0</i>

^aItalics denote studies of adolescents.

^bThe quality of the primary outcome measure is indicated by +/++/+++ (between brackets if the primary outcome measure is not specifically mentioned).

^cThe following symbols indicate effectiveness: 0 = no significant difference between active treatment and placebo, +/++/+++ = strength of the difference (with a positive effect of active treatment), () = effectiveness in secondary analysis.

^dRefers to cocaine, alcohol, and cannabis.

AARS, Adult ADHD Rating Scale; ADHD-RS, ADHD Rating Scale; AISRS, Adult ADHD Investigator Symptom Rating Scale; CAARS-O, Conners' Adult ADHD Rating Scales, Observer's Rating; CAARS-SV, Conners' Adult ADHD Rating Scales, Screening Version; CGI, Clinical Global Impression; Conners' HI Scale, Conners' Hyperactivity/Impulsivity Scale; MAS, mixed amphetamine salts; MMT, methadone maintenance treatment; OROS, osmotic-controlled release oral-delivery system; SUD, substance use disorder; TLFB, Timeline Followback; WRAADDS, Wender Reimherr Adult ADD Scale.