

Attention Deficit Hyperactivity Disorder (ADHD) and Substance Use Disorders

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Attention deficit hyperactivity disorder (ADHD) is a common childhood disorder that often continues to manifest symptoms into adulthood. In children and adults, this condition may contribute to addictive vulnerability. Several factors are common to the developmental psychopathology of these conditions, suggesting an underlying deficit in behavioral regulation as an explanation for this comorbidity. Developmentally, faulty learning processes or attempts to self-medicate dysfunctional behavior may contribute to the pathogenesis of substance use disorders. Substance abuse itself also may contribute to the development of attentional deficits and behavioral dysregulation through direct (eg, prenatal or self-inflicted exposures to neurotoxic substances) and indirect (eg, poverty, neglect, abuse) mechanisms. Because ADHD can be identified prior to the peak onset of substance use, effective treatment of this common disorder may reduce the development of substance use disorders. Adult ADHD may also contribute to the development and maintenance of substance use disorders. Substance abuse patients may particularly benefit from treatment of this comorbidity.

Introduction

Parents and providers are both very concerned about dramatic increases in the prescription of stimulant medication to children [1]. Many people, including treatment providers, wonder whether prescribing stimulants (also known as “speed”) to children may in itself promote the development of drug abuse. Some investigators have demonstrated that stimulant treatment of attention deficit hyperactivity disorder (ADHD) may actually reduce the developmental risk of substance use disorder (SUDs) [2••]. In adults, addiction treatment experts have also demonstrated that treatment of ADHD in the context of cocaine abuse may not only reduce ADHD symptoms, but it can also reduce cocaine use [3•].

However, the use of any type of psychiatric medication is not uncommonly met with resistance among patients and

providers of traditional substance abuse treatments [4,5]. Concern over the abuse of stimulant medications by patients and family members, when substance abuse is present, is not unreasonable given the potential of these medications for abuse by patients and their families, as well as diversion for profit [6]. Hence, the question of whether or not to prescribe stimulants to individuals with SUDs is a matter of great clinical significance.

This article seeks to review the developmental relationship among these common psychiatric disorders. The potential benefits and risks of earlier identification and treatment of these disorders will be considered, particularly as they relate to the development of addictive vulnerability among children and adults. The existing empirical evidence related to the treatment of ADHD in the context of comorbid SUDs will be reviewed. Finally, clinical factors specific to the diagnosis and treatment of these commonly comorbid conditions will be considered.

Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder is among the most common diagnoses of childhood. This syndrome is characterized by deficits in attention and increased levels of distractibility and activity (Table 1). Attention deficit hyperactivity disorder is one of four Disruptive Behavior Disorders that are listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) under disorders of childhood and adolescence. The other three disorders include Oppositional Defiant Disorder, Conduct Disorder, and Disruptive Behavior Disorder Not Otherwise Specified [7].

Approximately 5% of children in community-based epidemiologic surveys in the US meet criteria for this common, treatable disorder. Although it has been suggested that over-treatment of ADHD with stimulant medications is occurring in the US, there is little evidence for this. In fact, when carefully crafted psychopharmacologic treatment for ADHD is compared with a carefully crafted behavioral approach, medication treatment appears to be considerably more effective for the treatment of this disorder [8].

Attention deficit hyperactivity disorder is commonly comorbid with other psychiatric disorders, most particularly conduct disorder. Approximately 40% of children with ADHD also meet criteria for conduct disorder, and

Table 1. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for attention deficit hyperactivity disorder

- A. Either 1) or 2):
- 1) Six (or more) of the following symptoms of inattention that have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
Inattention
 - a) Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
 - b) Often has difficulty sustaining attention in task or play activities
 - c) Often does not seem to listen when spoken to directly
 - d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not because of oppositional behavior or failure to understand instructions)
 - e) Often has difficulty organizing tasks and activities
 - f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
 - g) Often loses things necessary for tasks and activities (eg, toys, school assignments, pencils, books, or tools)
 - h) Is often easily distracted by extraneous stimuli
 - i) Is often forgetful in daily activities
 - 2) Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level
Hyperactivity
 - a) Often fidgets with hands or feet in seat
 - b) Often leaves seat in classroom or in other situations in which remaining seated is expected
 - c) Often runs about or climbs excessively in situations in which it is appropriate (in adolescents or adults, may be limited to a subjective feeling of restlessness)
 - d) Often has difficulty playing or engaging in leisure activities quietly
 - e) Is often "on the go" or often acts as if "driven by a motor"
 - f) Often talks excessively
- Impulsivity
- g) Often blurts out answers before questions have been completed
 - h) Often has difficulty awaiting turn
 - i) Often interrupts or intrudes on others (eg, butts into conversation or games)
- B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7
- C. Some impairment from the symptoms is present in two or more settings (eg, at school and at home)
- D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning
- E. The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder, and are not better accounted for by another mental disorder (eg, mood disorder, anxiety disorder, dissociative disorder, or a personality disorder)
- Code based on type:
- Attention deficit hyperactivity disorder, combined type—if criteria A1 and A2 are met for at least 6 months
- Attention deficit hyperactivity disorder, predominantly inattentive type—if criterion A1 is met but criterion A2 is not met for at least 6 months
- Attention deficit hyperactivity disorder, predominantly hyperactive-impulsive type—if criterion A2 is met, but not criterion A1 is not met for at least 6 months

this particular comorbidity is particularly predictive of early onset substance use disorders and antisocial personality disorder in adulthood [9•]. Some investigators have suggested that this comorbidity is a distinct phenotype that indicates a high level of addictive vulnerability. Although there is some debate in the literature, ADHD alone appears to be a risk factor for the development of substance use disorders [2, 10•]. Moreover, at least one group has shown that treatment of ADHD can reduce risk of onset of substance use disorders to that of normal control individuals [2].

The Development of Substance Use Disorders

Many children experiment with substances of abuse, fewer develop substance-related problems, and a subset of these

children goes on to have chronic substance use disorders [11]. Understanding factors associated with normative substance use are not as likely to help explain SUDs, as are factors associated with the development of substance-related problems. Impaired behavioral learning may be involved in the failure of normal protective mechanisms in the pathogenesis of SUDs. For example, an attention deficit may cause a conceptual inability to determine long-term consequences of an action, which in turn may lead to a failure of delayed gratification and thereby increase the relative value of immediate gratification despite devastating long-term consequences [12]. The present-centeredness and impulsivity of substance abusers has been repeatedly described, as well as the relative difficulty with delayed gratification of current desires [13]. Developmentally, these concerns are particularly relevant to adolescent substance abuse [14].

Early exposure to substances of abuse is correlated with the development of early onset substance use disorders. Exposure to substances of abuse in certain individual contexts may enhance addictive vulnerability. For example, among children of alcoholics, behavioral undercontrol, emotional distress, and individual beliefs regarding alcohol use are highly associated with the development of alcohol use disorders [15]. Moreover, a relative lack of psychosocial protective factors such as prosocial activity, intolerance of deviance, and conventional peer models of behavior, are associated with greater problematic (vs normative) use of alcohol [16]. Faulty learning, or an inability to accurately conceptualize the long-term consequences of alcohol abuse, is a prime candidate for the explanation of the development of alcohol abuse in youth (and the acceptance of deviant behavior) who have been exposed to the aversive consequences of alcohol abuse through their parents' alcoholism. This conceptual difficulty might be compounded further through the dissociation of proactive peers (able to learn of the adverse consequences of substance use), and again through limited skills to cope with social failure, and even further through worsened negative affect.

Exposure to other substances of abuse such as cocaine during the prenatal period is also associated with behavioral dysregulation (especially impulsivity and inattention) and language disorder [17]. The attendant complications of alcoholism or cocaine abuse (poor nutrition, economic disadvantage, poor parenting, prematurity, additional substance abuse) make it difficult to control precisely for the effects of prenatal exposure to these substances [18]. Prenatal exposure to nicotine and alcohol has also been associated with disruptive behavior disorders among offspring [19,20]. Although it is difficult to ascertain whether genetic or environmental influences predominate in conferring attention problems to offspring of drug or alcohol abusing parents, it is clear that children of alcoholics or children of drug addicts, whether the mother or the father is affected, have a higher risk for the development of SUDs and a variety of disruptive behavior disorders.

Moreover, fundamental deficits in behavioral regulation (impulsivity, inattention) and in language ability are more common in children of drug addicts; these appear early in development, prior to the initiation of substance use. One syndrome of poor behavioral regulation specifically related to SUDs is conduct disorder. In a prospective study of youth at high risk for alcoholism, the presence of pre-adolescent conduct disorder is a powerful predictor of early adolescent cannabis abuse. This suggests that the development of conduct disorder mediates the development of SUDs in high-risk groups [21]. Conduct disorder has also been suggested to mediate the relationship between ADHD and SUDs [22]. Conversely, the single most robust risk factor for conduct disorder is hyperactivity observed during childhood [23•].

Developmentally, this relationship may have important implications. Deficits in behavioral regulation may lead to ADHD or conduct disorder, which may increase the risk of developing SUDs. Deficits in behavioral self-regulation are predictive of behaviors prodromal to adolescent substance abuse (particularly deviant peer relations) among children of alcoholics [24]. Studies of alcohol abusers also have prospectively linked deficits in behavioral regulation (eg, high novelty seeking) to the development of alcohol use; moreover, these traits appear to identify a group of alcohol abusers with an earlier onset of alcohol abuse [25,26]. Consequently, the identification of these traits may be particularly relevant to the pathogenesis, prevention, and treatment of adolescent SUDs.

More than a coincidental comorbidity, however, this subgroup of youth with ADHD and conduct disorder appears to represent an etiologically distinct, and particularly virulent form of disruptive behavior disorder, with a high risk for multiple adverse outcomes, including SUDs [27]. Aberrant function of self-regulatory capacity and affective systems are critical factors in the prediction, prevention, and treatment of both disruptive behavioral disorders [6] and early onset substance use disorders [9•,28]. It is possible that a common dysregulation of self-regulatory capacity underlies the developmental progression of both types of disorders for a majority of early-onset substance abusers.

One potential explanation for this association is an inherited dopaminergic dysfunction. Through studies of families affected by ADHD, a couple of research groups have found that the seven-repeat allele of the *DRD4* may be overrepresented in children with ADHD [29,30]. The overexpression of the dopamine transporter has also been implicated in the pathophysiology of ADHD. The 10-repeat allele of the dopamine transporter gene has been associated with ADHD [31,32]. Preliminary data suggest that this transporter variant is associated with a poor methylphenidate response [33]. In addition, further work has shown that dopamine transporter density is significantly higher in adults with ADHD compared to healthy control individuals [34]. Therefore, drugs that increase synaptic dopamine may counter this impairment in dopamine transmission. Because the mesolimbic dopaminergic pathway is considered to be the final common pathway for the addictive process, aberrant dopaminergic function is a leading neuropsychiatric explanation for the observed association between ADHD and addiction [35,36].

A controversial explanation for the observed association between ADHD and substance use is that stimulant exposure, even that prescribed by treatment providers, increases the likelihood of an individual developing a problem with stimulants. Theoretically, this risk could occur by 1) the process of behavioral sensitization or 2) augmented attempts at self-medication by individual patients. Adults diagnosed with ADHD in childhood,

who had used stimulant medication in childhood, have been found to be more likely to be daily smokers and tobacco-dependent than those who had not taken stimulants [37]. However, there may be a bias inherent in these comparisons; children who exhibit disturbed behavior are not only more likely to develop alcohol use disorders, they are also more likely to be identified for treatment [38]. Other studies, that compare children with ADHD who are treated with control groups of children with ADHD who are not treated with stimulants, suggest that treating ADHD children with stimulants *reduces* the risk for substance use disorders [2••,39]. For many children with ADHD, stimulant treatment results in reintegration in mainstream education, socialization and reduced substance use.

Adult Development

Nearly half of children with ADHD continue to manifest significant symptoms in adulthood. These deficits are pervasive and contribute to a cascade of social and occupational deficits that may increase liability toward substance use as a mechanism of coping [40]. For example, children with ADHD followed into adulthood are more likely to have completed less schooling, hold lower-ranking occupations, continue to suffer from poor self-esteem, have social skill deficits, and have antisocial personality disorder [41••]. Moreover, individuals with ADHD were more likely to have had their driver's license suspended, incurred more speeding violations, have quit or been fired from their job, and to have been married multiple times [42].

Attention deficit hyperactivity disorder appears to have multiple negative effects on substance use disorders, resulting in increased severity and treatment resistance. Attention deficit hyperactivity disorder itself may promote the transition from substance use to abuse. For example, adults with ADHD are more likely to transition from an alcohol use disorder to a drug use disorder, and continue to abuse substances following a period of substance dependence, compared with adults without ADHD [43]. People with ADHD also have a longer duration of having a substance use disorder and a slower remission rate [10•]. Individuals with cocaine abuse and a history of childhood ADHD have an earlier onset of regular cocaine use, more frequent and intense cocaine use, and greater lifetime treatment exposure [44]. To the extent that ADHD may increase the risk of and reduce the effectiveness of evidence-based treatments for substance use disorders, it is imperative that clinicians identify the presence of these commonly comorbid disorders [45].

Identifying Attention Deficit Hyperactivity Disorder Among Substance Abuse Patients

Identifying ADHD among children at risk for SUDs may help avert one of the most preventable causes of morbidity

and mortality among adolescents and adults today: substance abuse. However, identifying ADHD among adolescent and adults with substance use disorders is commonly complicated with a differential diagnosis that includes the effects of ongoing substance use, detoxification, and withdrawal. Moreover, there may at times be a secondary gain involved for sociopathic patients, who may intend to obtain the medication for abuse or diversionary purposes [6,9•]. Nonetheless, investigators suggest as many as 50% of adolescents in treatment may meet criteria for ADHD [46].

Because the diagnosis of ADHD was initially based on school-aged children, there are several developmental caveats clinicians need to consider in order to make the diagnosis in adolescents and adults. First, the DSM-IV definition of ADHD requires a history of symptoms prior to the age of 7, a criterion that is less readily assessed in adults with other symptoms of this disorder. It is not uncommon even for children to exhibit severely impairing ADHD symptoms without meeting this or other ADHD criteria. Some investigators have questioned this age at onset criterion, suggesting that it has low reliability [47,48]. Some clinical researchers have developed other criteria to define adult ADHD. The "Utah Criteria" [49] require at least one of the first two symptoms and four of the following to be present, including: 1) inattention or 2) hyperactivity 3) behavioral problems at school; 4) impulsivity; 5) overexcitability; and 6) temper outbursts.

Among substance abuse patients, it is important to discover the relationship between these symptoms and ongoing substance use, detoxification or prolonged withdrawal states. In this context, one method that clinicians may use is a timeline follow back method, which charts the appearance of attention deficit symptoms alongside periods of substance abuse. The senior author has observed that some individuals with cocaine dependence will have impairing ADHD-like symptoms that occur only after a period of regular drug use, but cannot recall having symptoms of ADHD in childhood [50].

There are, of course, developmental differences between assessing school aged children, adolescents and adults. Of note, there is a developmental reduction in activity with concomitant increases in ability to attend in individuals with and without ADHD. All psychiatrists, child-, adolescent-, and adult-based, need to consider the developmental appropriateness of each ADHD symptom within each developmental context. Just as there are arguments about how to define this syndrome in adulthood, investigators are trying to develop criteria to define this disorder during the preschool period [51]. Only an interviewer informed through subjective and objective data within an individual's particular developmental context can determine the maladaptive significance of symptoms of inattention, distractibility, or hyperactivity. For example, behaviors difficult to perform in childhood become routine as one grows through adolescence into

adulthood. Individuals learn ways to compensate for attention deficits, *eg*, keeping copious notes, obtaining less demanding jobs, avoiding potential distractions, and so forth. Future revisions of DSM-IV will need to develop new criteria that incorporate symptoms more relevant to the challenges encountered by adults [27].

Additional comorbidities may also complicate the picture, and contribute to attention deficits. Individuals with major depression may experience symptoms of inattention but are less likely to experience other symptoms that are associated with ADHD (*eg*, hyperactivity, talkativeness). Often adults with ADHD have first-degree relatives with ADHD. However, depression and bipolar illness are also over-represented in families of individuals diagnosed with ADHD [52,53]. Other disorders that should be considered, but are usually readily discriminated through a careful mental status examination, include psychotic and anxiety disorders. Because multiple other comorbidities may also impair attention, a comprehensive diagnostic assessment addressing psychiatric comorbidity and pertinent family history is needed prior to initiating any pharmacotherapy.

Increasingly, clinicians are beginning to recognize a syndrome of inattentiveness, distractibility, and hyperactivity that persists into adulthood. Several lines of evidence support the reliability and validity of this disorder during adulthood, and the interested reader is referred to more comprehensive reviews of the subject [49,54,55]. Fortunately, as clinical researchers seek to revise our diagnostic system, impairing disruptive behavior symptoms can be coded for people of all ages through using the attention deficit disorder not otherwise specified or the disruptive behavior disorder not otherwise specified classifications. Many leading ADHD investigators feel this is an underused category that offers clinicians a DSM-IV code for maladaptive symptoms that meet subthreshold criteria for full disorders [8].

Treatment

Attention deficit hyperactivity disorder symptoms may impair a patient's response to evidence-based treatments such as cognitive behavioral therapy, relapse prevention, or family therapy [45]. Because individuals with ADHD can be impulsive, they may more often drop out of treatment. As with youth who have concomitant learning and behavior problems, their behavior is more likely to be attributed to willful oppositional behavior than a neuropsychiatric disorder such as ADHD [23•]. The authors of this paper have clinically observed that through enhanced recognition and effective treatment of ADHD, these problems can be minimized.

Although treatment for substance abuse patients with adult ADHD can be categorized as pharmacologic or non-pharmacologic, interactions can occur between these types of treatment. In child and adult practice, both types of

treatment approaches are often used concomitantly. Initially, clinicians may attempt to use nonpharmacologic interventions (*eg*, parent management training in children). However, if these measures fail to improve symptoms, a pharmacologic trial may be added. There is evidence that pharmacologic treatment is considerably more robust than short-term behavioral therapy in remediating ADHD symptoms among school children. In some populations, using pharmacologic interventions to reduce ADHD symptoms, *eg*, distractibility or restlessness, may enhance the effectiveness of behavioral or other approaches.

These combined approaches may be particularly advantageous to youth with comorbid disruptive behavior disorders such as oppositional defiant disorder or conduct disorder, but they appear to be of limited additional value in treating ADHD alone [56,57••]. It should be noted that oppositional defiant disorder and conduct disorder appear on a developmental spectrum of antisocial behavior, culminating in antisocial personality disorder [6]. Hence, these combined treatments may be important therapeutic modalities for groups of adolescent and adults substance abusers where antisocial behavior is commonly encountered. Some parents and substance abuse treatment providers may prefer nonpharmacologic approaches as an initial management strategy. Independent of the sociocultural biases that may exist within these populations of adolescents or adults, the authors think it is important that the clinician carefully assess the potential risks and benefits of available treatments with the patient and family.

Pharmacotherapy for Attention Deficit Hyperactivity Disorder

Psychostimulants, particularly methylphenidate (MPH), are the most commonly prescribed and most effective medications for both child and adult ADHD [2••,27,57••]. The majority of studies carried out in adults have reported benefits from stimulants although the results have not been as robust as those found in children. The relative reduction in effectiveness could potentially be related to a more severe form of the disorder that continues into adulthood, as well as possibly being further down a developmental cascade of maladaptive forces secondary to a lifetime of ADHD.

The studies that have shown the best response to MPH in adults have used larger amounts in multiple doses during the day [58]. These findings are consistent with finding from the child literature, which demonstrate that carefully titrated psychostimulant treatment (three times per day dosing) is considerably superior to community treatment with stimulants (which is commonly both lower in quantity and frequency of dosing) [57]. The current availability of extended release delivery systems for methylphenidate provides once-daily dosing that demonstrates

behavioral effects equivalent to and, on some parental ratings, superior to three-times-daily dosing of standard preparations of methylphenidate [59].

A variety of nonstimulant medications have been used to treat ADHD (see [60•] for a more comprehensive review). In short, the only medications that have been demonstrated to reduce core ADHD symptoms in children are bupropion and desipramine. Bupropion may be particularly useful in the treatment of ADHD among adolescent and adult substance abusers. The use of desipramine, despite its proven effectiveness, is limited somewhat, because of the tendency of tricyclic antidepressants to increase the QTc interval, and several reports of sudden death in children treated with this medication. Although all of these deaths were associated with underlying heart defects, electrocardiograms are recommended by the American Academy of Child and Adolescent Psychiatry at initiation and at each dose change. Alpha-2-adrenergic agents such as clonidine have been shown to reduce hyperactivity and impulsivity, but have little, and possibly negative, affect on attention. Potentially promising agents include venlafaxine and beta-adrenergic blockers, although their effectiveness has not been demonstrated in controlled trials. Newer medications that may prove useful, but are not currently approved for use in the US, include norepinephrine reuptake inhibitors (*ie*, reboxetine and tomoxetine) and centrally acting anticholinesterases (*eg*, donepezil).

Nonstimulant medications have also been used to treat adult ADHD. As in adolescents, bupropion has shown a clinical advantage over placebo in reducing ADHD symptoms in adults with ADHD [61]. Some other medications that have been studied under double blind, placebo-controlled conditions for the treatment of adult ADHD include desipramine, tomoxetine, bupropion, and ABT-418, a selective cholinergic activating agent. Desipramine has been shown to significantly reduce ADHD symptoms, and appears to be better tolerated by adults, although electrocardiogram monitoring is still required [62]. Tomoxetine, an experimental noradrenergic reuptake inhibitor, also produced highly significant improvements in ADHD symptoms [63]. Pemoline has been shown to be more effective than placebo in treating both child and adult ADHD, but given the limited efficacy and tolerability of pemoline, and possible hepatic dysfunction (particularly in substance abusers and children), the authors recommend pemoline as a second-line treatment for ADHD [64].

One important consideration in selecting treatments for ADHD, particularly in substance abuse patients, is considering the overall diagnostic formulation. Comorbidity is particularly common among these patients. One group of disorders to consider is mood disorders, both unipolar and bipolar disorders. The advantage of desipramine, tomoxetine, and bupropion is that they are also used to treat depression. Another medication

approved for the treatment of depression that shows some promise for the treatment of adult ADHD is venlafaxine. However, this medication has only been evaluated in open trials [65,66], and further study under controlled conditions is needed. Consideration of hypomania or mania in the differential is an important step in the diagnostic formulation, however. There is considerable overlap between ADHD and manic symptoms; hence, a careful history may also identify bipolarity. However, bipolar disorder can co-occur with ADHD, and some groups report that the comorbidity may be as high as 25% in some clinically referred populations [2••].

Pharmacotherapy of Attention Deficit Hyperactivity Disorder in Substance Abuse Patients

In clinically referred samples of adolescent substance abuse patients, from 30% to 50% meet criteria for ADHD [9•]. Because many of these youth also have conduct disorder, they are at particularly high risk for life course persistent SUDS. Given the potential contribution of ADHD to the maintenance of substance use behaviors, as well as the possibility of attention deficits reducing treatment effectiveness, treatment of ADHD should be carefully considered by the clinician. After a patient is detoxified from a substance of abuse, and if the patient continues to demonstrate ADHD symptoms, there are several treatment options available.

Bupropion may be a first-line medication in this population, because of its safety, high tolerability, and limited abuse potential. In one open trial, bupropion was shown to reduce hyperactivity scores among nondepressed boys in a residential treatment program for delinquent substance abuse patients [67•]. In another open trial of adult substance abuse patients, bupropion reduced cocaine use and ADHD symptoms [68•]. These promising findings need to be replicated in larger, placebo-controlled trials. Particularly, because there is some indication that this medication may reduce drug use in certain sub-groups of drug abusers. For example, although in one double blind study of methadone maintained adults bupropion was not more effective than placebo, the authors found that among cocaine abusers with comorbid depression, those who received bupropion had a greater reduction in cocaine use than those who received placebo [69]. Further, the authors suggest that bupropion might be effective for cocaine abusers with adult ADHD. Although more research with double blind placebo-controlled trials is clearly needed to confirm these findings, the authors found that this medication helps a substantial minority of adolescents and adults seeking substance abuse treatment.

Desipramine is well tolerated among adults who are currently using cocaine. Several double blind placebo-controlled treatment trials have been carried out in cocaine abusers seeking treatment without any untoward side

effects. Findings from laboratory studies also support that there are few clinically significant cardiovascular effects when cocaine is administered to individuals maintained on desipramine [70]. However, the effectiveness of desipramine in reducing cocaine use without attendant comorbidity is questionable [71,72]. In cases where depression and attention deficit disorder is present, even in the context of cocaine abuse, a strong case can be made for a desipramine trial. However, a more careful assessment of potential risks and benefits is required for the use of this medication in adolescents, because of the concerns described.

Still, the most robust treatment for ADHD is stimulant medication. Two double blind studies comparing MPH to placebo for the treatment of adult ADHD did include a small number of substance abusers [58,73]. In these studies, ADHD appeared to be a predictor of treatment response, but substance use was not assessed in this study. Methylphenidate does not appear to have an effect on cocaine use among individuals without ADHD [74]. The most common side effects were jitteriness and decreased appetite, but the medication was, in general, well tolerated, and discontinuation of treatment was not required. In a recently completed laboratory study, the authors' group found that minimal untoward cardiovascular effects occurred when repeated doses of cocaine were given to nontreatment-seeking cocaine abusers with adult ADHD who were maintained on sustained-release MPH [75] (note: sustained release preparations of methylphenidate are not equivalent to extended release preparations, and the former offer only a modest observable increase in the duration of behavioral effect compared to the latter [59]).

There is promising data suggesting that MPH (in the sustained-release formulation) is a useful treatment for treatment seeking cocaine abusers with ADHD [76]. In this study, which used divided daily doses ranging from 40 to 80 mg per day of sustained-release MPH, both ADHD symptoms and cocaine use significantly decreased. Weekly individual relapse prevention therapy was also provided. Recent pilot studies also support that MPH might reduce cocaine use and ADHD symptoms [77]. However, these are open trials, and double blind controlled trials are clearly warranted. No studies that used the extended release preparations of methylphenidate were found in a literature search. These preparations, because of the possible enhancement of compliance and extension of behavioral effect may prove to be more useful in reducing drug use over the entire day.

Stimulants are usually approached with caution with this population, because of their abuse potential, as well as their potential for diversion for profit. One recent technological development that the authors feel enhances the ability to monitor these prescriptions is the availability of extended, once-daily preparations of methylphenidate. This appears to enhance the ability of clinicians, parents or guardians to monitor the use of these medications. These

medications may also reduce the embarrassment that accompanies the need for noontime dosing at high school, which many youth dislike. Although the authors have used these medications with both adolescents and adults with substance use disorders, no open or controlled trials of their use with substance abusers were found with a literature search. The authors think that more research is needed to address the question of whether the prescription of the extended release methylphenidate is an effective treatment in reducing ADHD symptoms among adolescent or adult substance abusers. Moreover, further research is needed in both children and adults to assess whether such delivery systems can improve compliance and reduce abuse or diversion.

A history of amphetamine abuse may be a relative contraindication or stimulant treatment. However, whether treatment with amphetamines enhances cocaine craving or cocaine abuse remains an empirical question. Although one research group reported that methylphenidate increased cocaine craving and use among cocaine abusers without ADHD [78], this finding has not been substantiated by other investigators [76,79].

There are no widely accepted guidelines for the appropriate pharmacologic treatment of ADHD in the presence of substance abuse disorders, for adolescents or adults. Nonstimulant medications such as bupropion, venlafaxine, or desipramine are usually considered second-line treatments for ADHD. However, for adolescents or adults with a current or lifetime history of a substance use disorder, an initial prescription of a less robust, but possibly safer, second-line treatment may be indicated. If substantial maladaptive ADHD symptoms remain, a clinician should carefully consider a stimulant trial. The safety of such a trial may be enhanced through careful monitoring of the prescriptions, frequent visits and urinalyses, and possibly the use of once-daily medication that can be monitored by a parent, guardian or significant other.

Nonpharmacologic Interventions

Nonpharmacologic approaches to ADHD treatment take on a particular significance in treating ADHD among individuals with substance use disorders. This is not difficult to understand, given that in many cases the self-administration of drugs of abuse has become a problem that eclipsed the original problem of ADHD. Nonetheless, compared with pharmacologic treatment literature, there are even fewer clinical data regarding what nonpharmacologic approaches work best for substance abusers with ADHD. Similar to the treatment of substance abuse patients with other psychiatric disorders, it is likely that concurrently treating both the substance use disorder and ADHD symptoms is more likely to produce a positive treatment outcome than treating only one disorder. The psychotherapeutic approaches, which appear to be most useful in the treatment of ADHD, include behavioral, cognitive-

behavioral, and combined behavioral-medication approaches [80,81].

In the most comprehensive treatment study of ADHD to date, the National Institute of Mental Health sponsored Multimodal Treatment of ADHD (MTA) study, 579 children were randomly assigned to one of four groups: 1) routine community care; 2) monthly medication management (usually methylphenidate three times daily); 3) intensive behavioral treatment; or 4) a combination of 2 and 3. The largest benefits were observed among children receiving methylphenidate three times daily, regardless of whether the children were in the combined or medication only groups [57••]. Although it is clear that medication provided the most robust treatment for ADHD, there were groups who appeared to differentially benefit from behavioral therapy in this study. Of most relevance to this article, children with additional disruptive comorbidity, *ie*, oppositional defiant or conduct disorder, appeared to benefit more from the combined treatment compared with the medication only treatment.

These data may have particular relevance to children at high risk for substance use disorders, such as those with ADHD and conduct disorder, and may even have relevance for treatment seeking populations of substance abusers. Further research in this area needs to test the hypothesis that those children with comorbid ADHD and conduct disorder benefit from a multimodal or combined behavioral or medication approach. Studies of recidivistic delinquents strongly suggest the need for such multimodal treatments [6]. Testing this hypothesis among children at high risk for substance use disorders may help to identify proximal, remediable risk factors in the development of substance use disorder. In our group, psychotherapy with adult substance abuse patients with comorbid ADHD has suggested that manual-based relapse prevention therapies (evidence-based treatments for substance abuse) can be readily adapted for this group. Attention deficit hyperactivity disorder-related limitation can be countered in treatment by providing tangible coping skills and strategies, many of which are incorporated in the relapse prevention model [82]. These data suggest the need for the development and testing of behavioral strategies to enhance relapse prevention among substance abusers with ADHD [83–85].

Conclusions

Attention deficit hyperactivity disorder is an important, potentially remediable, factor that can contribute to addictive vulnerability across the life span. Although advances have been made in the identification and treatment of this disorder among children, adolescents, and adults, there is relatively little research on the treatment of ADHD among substance abusing adolescents or adults. Features of the addictive process complicate treatment with the most

robust ADHD treatments, *ie*, stimulants. More research is needed to evaluate whether newer psychopharmacologic agents (*eg*, noradrenergic reuptake inhibitors, centrally acting cholinergic agents) or new delivery systems (*ie*, extended release methylphenidate) can reduce ADHD and substance abuse among these comorbid populations. Similarly, little is known about the behavioral treatment of ADHD and comorbid disruptive behavior disorders among high-risk children, or the behavioral treatment of ADHD among substance abuse patients. There is some evidence to suggest that these groups may benefit differentially from combined treatments for these disorders. Future research should include the development of manual-based behavioral therapies to reduce ADHD, and disruptive behavior symptoms among those at high risk for and seeking treatment for substance use disorders. Finally, comprehensive multimodal trials such as the MTA study may serve as a model for the study of ADHD among adolescents or adults with SUDs. This would help treatment providers to develop evidence-based treatments for these commonly comorbid problems.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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