

ARTICLE

# ADHD with comorbid substance use disorder: review of treatment

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## SUMMARY

Substance use disorders are a frequent comorbidity in adult attention-deficit hyperactivity disorder (ADHD). This review discusses the relationship between adult ADHD and substance use disorder, including use of licit and illicit substances such as nicotine, alcohol, cocaine and cannabis. We discuss treatment studies in this area and provide a treatment algorithm to guide clinicians in the management of adult ADHD comorbid with different forms and severities of substance use disorder.

## DECLARATION OF INTEREST

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Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects 3–7% of children (Wilens 2004). Prospective longitudinal studies show persistence of the disorder in 10–20% of adults diagnosed with ADHD in childhood, and a further 40–60% of patients experience partial remission, with persistence of some symptoms and significant clinical impairments (Barkley 2008). Population studies estimate the prevalence of adult ADHD at between 3.4 and 4.4% (Kessler 2006). The DSM-IV (American Psychiatric Association 1994) and the ICD-10 (World Health Organization 1993) criteria are widely used to diagnose ADHD in adults. The 2008 National Institute for Health and Clinical Excellence (NICE) guidelines provide evidence for the validity of ADHD diagnosis in children and adults and make recommendations for its diagnosis and management. Detailed description of clinical diagnosis and management of adult ADHD is given elsewhere (Weiss 2003).

Substance use disorders are common in adults with ADHD (Kessler 2006; Box 1). Prospective studies (Molina 2003) and population-based surveys (Kessler 2006) clearly demonstrate a higher prevalence of substance use disorder in individuals with ADHD. Likewise, the prevalence of ADHD is substantially higher in adolescents

and adults seeking treatment for substance use disorder (Schubiner 2000).

## Methodology

This review discusses the relationship between substance use disorder and adult ADHD. We performed a comprehensive search of Medline and PsycINFO databases using the search terms 'attention deficit hyperactivity disorder', 'substance related disorder', 'substance misuse' and 'street drugs' and checked the reference lists of identified articles. We also searched the internet using Google, as well as searching psychiatry textbooks, published and unpublished treatment guidelines and conference proceedings by hand. To improve the clinical relevance we considered use of both licit and illicit substances, including nicotine, alcohol, cocaine and cannabis. The studies reviewed in our article used standardised criteria from DSM-III, DSM-III-TR, DSM-IV or ICD-10 (American Psychiatric Association 1980, 1987, 1994; World Health Organization 1993) to diagnose adolescents or adults with ADHD and comorbid substance use disorder.

## Relationship between substance use disorder and ADHD

Several longitudinal studies of children and adolescents with ADHD point to a greater risk of

### BOX 1 Main clinical issues of ADHD comorbid with substance misuse

- Substance use disorders are a frequent comorbidity in ADHD
- Significant challenges exist in assessing and treating ADHD in the context of substance use disorder comorbidity
- No clear treatment guidelines and care pathways exist to guide clinicians to manage ADHD with comorbid substance use disorder
- Issues in relation to exacerbation of substance use disorder, future risk of substance misuse and diversion of psychostimulants complicate treatment

### BOX 2 Relationship between ADHD and substance use disorder

- ADHD greatly elevates risk for substance use and misuse
- High novelty seeking trait, self-medication for ADHD symptoms and the presence of conduct disorder and bipolar disorder are risk factors for substance misuse in adult ADHD
- Patients with ADHD and substance use disorder tend to commence early and experiment more freely with substance misuse
- Growing up with ADHD confers a greater risk for using alcohol and tobacco, whereas clinic-referred adults with ADHD seem more likely to use marijuana, cocaine and LSD
- Substance use may be considered as a form of self-medication for patients with ADHD

developing substance use disorder in adolescence and adulthood as compared with matched controls (Molina 2003; Biederman 2006). Factors such as high novelty seeking trait, self-medication for ADHD symptoms (Asherson 2005) and comorbid disorders such as conduct disorder (Milberger 1997; Molina 2003) and bipolar disorder (Biederman 1997) increase the risk of developing substance use disorder in people with ADHD (Box 2).

Patients with ADHD and substance use disorders tend to commence early and experiment more freely with substance misuse compared with patients with substance use disorder without ADHD (Krause 2002a). Two recent studies, the UMASS project and Milwaukee study (Barkley 2008) demonstrate important findings. Compared with matched controls, adults with ADHD were more likely to be past or current users of substances and used these substances in greater amounts. They were also more likely to receive treatment for previous alcohol and drug use disorders. The UMASS project and the Milwaukee study further demonstrate that children growing up with ADHD may carry a greater risk for using alcohol and tobacco, while clinic-referred adults with ADHD seem more likely to use marijuana, cocaine and lysergic acid diethylamide (LSD).

### Substances most commonly used by adults with ADHD (Box 3)

#### Nicotine

Studies in both adults and adolescents have found ADHD to be associated with earlier initiation of regular cigarette smoking and higher rates of lifetime smoking (41–42% v. 26% for

ADHD and non-ADHD respectively) (Pomerleau 1995). Significant associations between ADHD symptoms and cigarette smoking have been found in both general population (Kollins 2005) and longitudinal studies (Milberger 1997; Molina 2003). Attention-deficit hyperactivity disorder has been shown to be an independent risk factor for tobacco use specifically in clinical and high-risk samples, even after controlling for comorbid conduct disorder (Milberger 1997; Molina 2003). Milberger *et al* (1997) followed 6- to 17-year-olds with and without ADHD for 4 years and found that ADHD was specifically associated with a higher risk of initiating cigarette smoking even when controlling for social class, psychiatric comorbidity and intelligence.

Factors such as inattention and deficits in executive functioning (Molina 2003), hyperactive/impulsive symptoms (Fuemmeler 2007), novelty-seeking traits (Tercyak 2003) and dysregulation of dopaminergic/nicotinic and acetylcholinergic circuits have been proposed to explain ADHD–smoking comorbidity. Two literature reviews (McClernon 2008; Glass 2010) provide evidence for the importance of cognitive, social, psychobiological and genetic factors in understanding the association between ADHD and cigarette smoking.

Clinical observations have revealed improvement of attention, concentration and impulse control with nicotine (Gehricke 2006) and several lines of evidence suggest that nicotine may be useful in treating ADHD symptoms (Newhouse 2008).

Given that nicotine has been shown to reduce ADHD symptoms, smoking cessation may be more

### BOX 3 ADHD and substance use

- Studies in both adults and adolescents have found ADHD to be associated with earlier initiation and higher rates of lifetime substance use (nicotine 41–42%, alcohol 33–44%, cocaine 10–35%, cannabis 51%, opiates 16–19%)
- ADHD has been shown to be an independent risk factor for tobacco use specifically in clinical and high-risk samples, even after controlling for comorbid conduct disorder
- Substance use in ADHD may be considered as a form of self-medication for patients with ADHD. Clinical observations have revealed that patients with ADHD with substance use disorder often demonstrate an improvement of ADHD symptoms
- Given that some substances have been shown to reduce ADHD symptoms, abstinence may be more difficult for adults with ADHD

difficult for adults with ADHD (Pomerleau 2003). A controlled laboratory study demonstrated that nicotine abstinence among smokers with ADHD is associated with greater worsening of attention and response inhibition than among those without ADHD (McClernon 2008). In another study of over 400 adult participants in smoking cessation treatment studies, childhood ADHD diagnosis was significantly associated with treatment failure (Humfleet 2005).

### Alcohol

Several studies have documented a high incidence (33–44%) of alcohol misuse or dependence in adults with ADHD (Biederman 1998; Rasmussen 2000). Likewise, an increased prevalence of childhood and persistent ADHD is noted in alcohol-dependent adults (Krause 2002b).

However, it is uncertain whether ADHD predicts the development of alcohol use disorders. A Danish longitudinal study (Knop 2009) designed to identify antecedent predictors of adult male alcoholism selected 223 sons of alcoholic fathers and 106 matched sons of non-alcoholic fathers from a Danish cohort ( $n=9125$ ). The study showed that: paternal risk did not predict adult alcohol dependence; ADHD comorbid with conduct disorder was the strongest predictor of later alcohol dependence; and that each measure (ADHD and conduct disorder) independently predicted a measure of lifetime alcoholism severity. Other long-term follow-up studies conducted in adolescents and young adults, however, have found no increased risk for alcohol use disorders in individuals with ADHD (Molina 2003) or revealed mixed findings. In a longitudinal study, Molina *et al* (2007) found that childhood ADHD predicts heavy drinking, symptoms of alcohol use disorders, and alcohol use disorders for 15- to 17-year-olds, but not 11- to 14-year-olds or 18- to 25-year-olds.

### Cocaine

Studies have reported prevalence rates of 10–35% of childhood ADHD in treatment-seeking cocaine users (Carroll 1993; Levin 1998). Cocaine users who had childhood ADHD are younger at presentation for treatment and report more severe substance use, more frequent and intense cocaine use, and intranasal or intravenous use of cocaine (Carroll 1993). In the UMMAS study of clinic-referred adults (Barkley 2008), cocaine use was specifically associated with ADHD. The study revealed that the risk for cocaine use was related to higher ADHD symptoms, lower IQ and greater criminal diversity scores. Clinical

observations have revealed that patients with ADHD and comorbid cocaine addiction often show an improvement of ADHD symptoms. The ‘self-treatment’ hypothesis is supported by studies reporting marked reduction in ADHD symptoms after cocaine consumption (Volkow 2003). Pathophysiologically, this may be explained by the dopaminergic action of cocaine reducing the core symptoms of ADHD.

### Cannabis

Torgersen *et al* (2006) reported lifetime and current rates of cannabis misuse of 51% and 36% respectively for their sample of 45 adults with ADHD. Molina and colleagues (2007) described an analysis of the Multimodal Treatment Study of Children with ADHD at the 24- and 36-month time points comparing individuals with ADHD with a control group without ADHD. At both the 24- and 36-month time point the group with ADHD was found to have significantly higher rates of cannabis use along with nicotine and alcohol (ADHD: 3.0%; no ADHD: 0%). A 25-year prospective longitudinal study of a birth cohort of New Zealand children ( $n=1265$ ) showed a significant association between cannabis use and increasing self-reported symptoms of adult ADHD at age 25 (Fergusson 2008).

Few studies have examined the relationship between cannabis use and ADHD. Adriani *et al* (2003) gave evidence that cannabinoid agonists reduce hyperactivity in a spontaneously hypertensive rat strain, which is regarded as a validated animal model for ADHD. Aharonovich and colleagues (2006) found significantly better treatment retention of cocaine-dependent patients with comorbid ADHD among moderate users of cannabis compared with abstainers or heavy users. The relationship between cannabis use and ADHD remains unclear and more empirical work is required to understand mechanisms determining this comorbidity.

### Opioids

There are very few studies examining the relationship between ADHD and opioid use disorder. Existing data from retrospective and prospective studies, however, suggest high rates of ADHD (16–19%) in treatment-seeking chronic opioid users (King 1999; Torgersen 2006).

### Caffeine

Caffeine is a popular psychostimulant consumed in most parts of the world. Clinical observations reveal increased consumption of caffeine in the ADHD population. Adults presenting with ADHD

tend to give an account of regular and increased consumption of caffeine through beverages such as tea, coffee, coke and energy drinks with high caffeine content. Caffeine in moderate amounts produces increased alertness and elevated mood (Cox 1983). In a literature review, Ross & Ross (1982) concluded that caffeine may be a viable treatment alternative for ADHD when other drugs must be discontinued due to side-effects. Ross & Ross (1982) also estimated a therapeutic dose of caffeine in children to be between 100 and 150 mg of caffeine, equivalent to 6 mg of dextroamphetamine. However, the relationship between caffeine and ADHD remains unclear and further studies are warranted to elucidate patterns of use and efficacy of caffeine in controlling ADHD symptoms.

## Treatment studies in ADHD with substance use disorder

### Psychostimulants

#### Methylphenidate

Several meta-analyses of randomised clinical trials (Koesters 2009; Faraone 2010) and evidence-based guidelines suggest that stimulants should be the first option for treatment for adult ADHD (Nutt 2007; National Institute for Health and

Clinical Excellence 2008). However, most ADHD treatment studies typically exclude individuals with substance use disorder and it would be difficult to extrapolate evidence derived from these studies to this population with a dual diagnosis of ADHD and substance use disorder (Szobot 2008). Koesters and colleagues (2009) performed a meta-analysis of clinical trials comparing methylphenidate with placebo in adult ADHD. In a subgroup analysis, four randomised controlled double-blind studies were identified that addressed the efficacy of methylphenidate in adults with ADHD and comorbid substance use disorders (Table 1). Three studies had a parallel group design (Schubiner 2002; Levin 2006, 2007) and one study (Carpentier 2005) used a cross-over design. There was large variability of treatment duration (2–14 weeks) and mean daily dose (34–79 mg). The meta-analysis of ADHD with substance use disorder studies (Koesters 2009) yielded an overall effect size of near zero (0.08; 95% CI –0.20 to 0.35). All four studies demonstrated no significant difference in ADHD or substance use symptoms with methylphenidate compared with placebo, although in one study (Schubiner 2002) physician and self-ratings taken at various times showed significant improvement in some

**TABLE 1** Treatment studies for stimulants/non-stimulants in attention-deficit hyperactivity disorder (ADHD) comorbid with substance use disorders

Study	Design	Intervention (duration of active treatment)	Drug of misuse	<i>n</i>	Results
Levin (2007)	Parallel double-blind	Methylphenidate (14 weeks)	Cocaine	106	ADHD symptoms: no significant difference between groups Substance use disorder symptoms: decrease in the probability of cocaine-positive urine samples in the methylphenidate group compared with the placebo group
Levin (2006)	Parallel double-blind	Methylphenidate or bupropion (10 weeks)	Methadone/cocaine	98	ADHD symptoms: no significant difference between groups Substance use disorder symptoms: no significant difference between groups
Carpentier (2005)	Cross-over double-blind	Methylphenidate (2 weeks)	Various	25	ADHD symptoms: no significant difference between groups Substance use disorder symptoms: not addressed
Schubiner (2002)	Parallel double-blind	Methylphenidate (13 weeks)	Cocaine	48	ADHD symptoms: no significant difference between groups Substance use disorder symptoms: no group differences
Wilens (2008a)	Parallel double-blind	Atomoxetine (12 weeks)	Alcohol	147	ADHD symptoms: significant improvement compared with placebo group Substance use disorder symptoms: inconsistent effects on drinking
Thurstone (2010)	Parallel double-blind	Atomoxetine (12 weeks)	Various	70	ADHD symptoms: no significant difference between groups Substance use disorder symptoms: no group differences
Levin (2002)	Open label	Bupropion (12 weeks)	Cocaine	11	ADHD symptoms: significant improvement Substance use disorder symptoms: significant reductions in self-reported cocaine use, cravings and positive toxicology
Solhkhah (2001)	Open label	Bupropion (6 weeks)	Various	14	ADHD symptoms: significant improvement Substance use disorder symptoms: significant reduction
Wilens (2010)	Open label	Bupropion (6 weeks)	Various	32	ADHD symptoms: significant improvement Substance use disorder symptoms: no significant reduction in severity
Riggs (2004)	Parallel double-blind	Pemoline (12 weeks)	Various	69	ADHD symptoms: significant improvement but no difference between groups in the intent-to-treat analysis Substance use disorder symptoms: no group differences

ADHD symptoms in the methylphenidate group. Another study (Levin 2007) reported a significant decrease in the probability of cocaine-positive urine samples with methylphenidate compared with placebo. All four studies recruited their study samples from treatment centres, so the results may not be representative of the general population (Royal Australasian College of Physicians 2009). None of the studies found serious adverse events as a result of the treatment, nor did the substance use disorder worsen because of the use of a stimulant (Royal Australasian College of Physicians 2009).

### Amphetamines

Randomised placebo-controlled trials demonstrate superior efficacy of amphetamines in adults with ADHD (Torgersen 2008) and in treatment of cocaine dependence (Grabowski 2004a). Our literature search did not find any studies evaluating the efficacy of amphetamines in ADHD with substance use disorder.

### Pemoline

Pemoline is a psychostimulant that acts through dopamine mechanisms. Riggs *et al* (2004) conducted a 12-week randomised controlled trial (RCT) to study the efficacy of pemoline in adolescents with ADHD and comorbid conduct disorder and substance use disorder (Table 1). The study found a significant difference in ADHD symptoms with pemoline treatment compared with placebo. However, despite efficacy for ADHD, pemoline did not have an impact on substance use disorder or conduct disorder. Pemoline is no longer commonly used in treatment of ADHD because of its association with liver toxicity.

### Modafinil

Modafinil is an analeptic drug approved for the treatment of narcolepsy, shift work sleep disorder and excessive daytime sleepiness associated with obstructive sleep apnoea. Modafinil, like other stimulants, increases the release of monoamines, specifically the catecholamines noradrenaline and dopamine, from the synaptic terminals. Modafinil has demonstrated dose-related positive effects in reducing impulsive responding in normal volunteers and in patients with ADHD (Turner 2004). A double-blind, placebo-controlled trial in 62 cocaine-dependent men and women reported increased cocaine abstinence in the modafinil group (Dackis 2005). Our literature search, however, did not reveal any studies specifically evaluating modafinil in ADHD with substance use disorder.

## Non-stimulants

### Atomoxetine

Atomoxetine is a highly specific noradrenergic reuptake inhibitor with no misuse liability (Heil 2002). Its efficacy in ADHD is clearly demonstrated in two 10-week double-blind, randomised controlled studies in adults ( $n=536$ ) with ADHD (Michelson 2003). However, studies addressing efficacy of atomoxetine in patients with ADHD and comorbid substance use disorders are very limited (Table 1). A 3-month double-blind, placebo-controlled study of atomoxetine in adults with ADHD and comorbid alcohol use disorder found clinically significant improvement in ADHD symptoms but inconsistent effects on drinking (Wilens 2008a). Thurstone *et al* (2010) explored the impact of atomoxetine on substance use in an RCT involving 70 adolescents with ADHD. Participants received atomoxetine and cognitive-behavioural therapy (CBT) or placebo and CBT. Although the group receiving atomoxetine and CBT showed an improvement in scores on the DSM-IV ADHD checklist, this was not statistically significant compared with the placebo group.

Atomoxetine has also gained attention in the treatment of nicotine withdrawal. Ray *et al* (2009) studied the effects of atomoxetine on subjective and neurocognitive symptoms of nicotine abstinence. The drug was reported to reduce subjective nicotine withdrawal symptoms and self-reported smoking urges.

### Bupropion

Bupropion is an atypical antidepressant that acts as a noradrenaline and dopamine reuptake inhibitor, and nicotinic antagonist (Slemmer 2000). It is considered safer as it is less likely to be misused (Griffith 1983) and several studies have demonstrated efficacy of bupropion in the treatment of ADHD with comorbid substance misuse (Table 1). In a 5-week open trial, bupropion was shown to reduce attention and hyperactivity scores among 13 adolescents with conduct disorder in a residential programme for patients who misuse substances (Riggs 1998). Three other open clinical trials have shown moderate reduction in ADHD symptoms and substance misuse (Solhkhah 2001; Levin 2002; Prince 2002). In a 12-week single-blind trial of bupropion (Levin 2002), patients reported significant reductions in attention difficulties, hyperactivity and impulsivity. Self-reported cocaine use, cocaine craving and cocaine-positive toxicologies also decreased significantly. This study concluded that bupropion may be as effective as methylphenidate when combined with

relapse prevention therapy, for cocaine misusers with adult ADHD. Conversely, in a 12-week placebo-controlled trial (Levin 2006), sustained-release bupropion did not provide a clear advantage over placebo in reducing ADHD symptoms or additional cocaine use in patients on methadone maintenance treatment. Results from an open trial (Wilens 2010) suggest that in adults with ADHD and substance use disorder, treatment with sustained-release bupropion is associated with clinically significant improvements in ADHD, but not in substance use disorder.

### Psychological intervention studies

Good evidence of the effects of psychotherapy in adults is sparse (Nutt 2007), but research supports the use of cognitive-behavioural methods for treating adult ADHD (Young 2007; Knouse 2010; Solanto 2010). Whatever evidence exists, it is difficult to extrapolate this evidence to the substance use disorder population, as most of these published studies evaluating efficacy of psychotherapy in ADHD exclude patients with substance use disorder.

Literature indicates efficacy for both individual and group CBT in substance use disorder (Liddle 2008). Structured, adapted psychotherapies that incorporate motivational enhancement, CBT and/or contingency management to combat substance use disorder can be very useful in treating patients with ADHD and comorbid substance use disorder. In the UK, the Young-Bramham Programme is an integrated programme for understanding ADHD, adjusting to the diagnosis and developing skills to cope with symptoms and associated impairments, including substance use disorder. The programme offers techniques based on psychoeducation, motivational interviewing, cognitive remediation and CBT (Young 2007).

### Diagnostic assessment

It is important to recognise the challenges inherent in assessing ADHD in the context of comorbidity (Box 4). A study exploring patterns of communication between physicians and patients with ADHD and depression concluded that psychiatrists treating adult patients with depression may not recognise ADHD (Dodson 2010). Given the overlap between symptoms associated with multiple psychiatric conditions, it is important to ensure that potential comorbidities are recognised, discussed and addressed.

Patients presenting for treatment of substance use disorder should be screened for the presence of ADHD symptoms. Screening instruments for adult ADHD (Barkley 1998; Conners 1998;

#### BOX 4 Assessment of ADHD and substance use disorder

- Patients presenting with substance use disorder should be screened for presence of ADHD
- Screening instruments for adult ADHD can be invaluable tools in the assessment of this group
- Assessment of these individuals should include current and childhood history of ADHD symptoms, detailed history of current and past substance use, previous treatments, and psychiatric, family and forensic history
- At least 1 month of abstinence is useful for accurate and reliable assessment for ADHD symptoms
- It is imperative to watch for signs of possible misuse, such as missed appointments, and signs of possible diversion, such as repeated requests for higher doses and a pattern of 'lost' prescriptions
- It is important to exclude high-risk situations (e.g. comorbid antisocial personality disorder, strong forensic history and family member or peers with substance use disorder)

Kessler 2005; Box 5) can be invaluable tools in the assessment of this group (Rosler 2006). It is important to bear in mind that abstinence from drug use may be required to evaluate ADHD symptoms properly. At least 1 month of abstinence is useful in accurately and reliably assessing for ADHD symptoms (Brown 2009).

A careful evaluation and assessment of these individuals should include history of attention deficit, impulsivity or hyperactivity symptoms in childhood, current ADHD symptoms, substance use, treatments, psychiatric disorders, and a family and forensic history. A comprehensive psychosocial assessment will help to understand particular strengths and difficulties of the individual in various domains.

### Treatment considerations

Exacerbation of current substance use disorder, future risk of substance misuse and diversion of psychostimulants complicate treatment of ADHD comorbid with substance use disorder. Evidence so far does not suggest that treating ADHD pharmacologically with stimulants during active substance use disorder exacerbates the disorder.

#### BOX 5 Screening instruments for adult ADHD

- Barkley Adult ADHD Rating Scale (Barkley 1998)
- Conners Adult ADHD Rating Scale (Conners 1998)
- Adult ADHD Self-Report Scale (ASRS) (Kessler 2005)

Grabowski *et al* (2004b) reviewed the data on use of stimulants as a treatment for cocaine addiction. Methylphenidate and amphetamine were variably effective in reducing cocaine use compared with placebo and did not exacerbate any aspects of cocaine addiction. In a meta-analysis using data from six studies (five prospective longitudinal studies and one retrospective study) Wilens *et al* (2003) reported a 1.9-fold reduction in risk of substance use disorders in individuals with ADHD who had taken stimulant medications compared with similar individuals who had not taken such medications. The authors, however, identified several limitations of their meta-analysis, including the small number of studies available and inherent confounding factors that may vary between studies, such as severity of ADHD and the presence/absence of comorbidities. Several longitudinal studies (Molina 2007; Barkley 2008; Biederman 2008) found no significant effect of stimulant treatment, age or duration of stimulant treatment on the development of substance misuse.

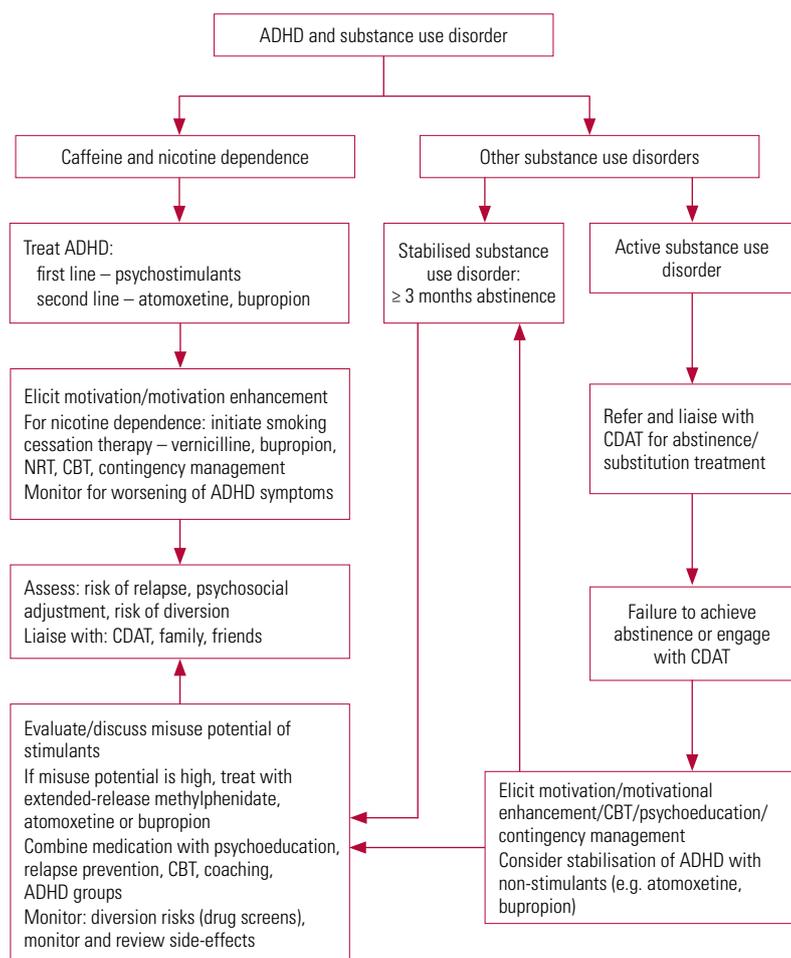
If a stimulant medication is prescribed, there is an important concern regarding its potential for misuse or diversion in this population. A systematic review (Wilens 2008b) found that 5–9% of school students and 5–35% of college students in the USA had used a non-prescribed stimulant over the previous 12 months. Between 16 and 29% of students with stimulant prescriptions had at some time been asked to give, sell or trade their medications. The reasons individuals reported for misusing stimulants were to enhance performance, self-medicate for ADHD symptoms and for their euphorogenic effects (immediate-release stimulants only).

Newer extended-release stimulants and pro-drug formulations minimise the risk of misuse and diversion of drugs (Spencer 2006). Lisdexamfetamine dimesylate (LDX) is the first long-acting prodrug stimulant (Faraone 2008). The structure of LDX (covalently bonded d-amphetamine and l-lysine) prevents mechanical drug tampering such as crushing (Faraone 2008). Following oral ingestion, it is hydrolysed into l-lysine and active d-amphetamine, which is responsible for the therapeutic effect (Faraone 2008). Preliminary evidence suggests the potential for reduced misuse liability of orally and intravenously administered LDX compared with d-amphetamine (Jasinski 2009).

## Management

Therapeutic interventions for ADHD and substance use disorder are multimodal with interventions from addiction modalities (drugs and alcohol service, Alcoholics Anonymous, Narcotics Anonymous), psychotherapeutic modalities (behavioural and cognitive therapies) and pharmacotherapy. On the basis of our literature review and the current evidence in this area we propose an algorithm to guide clinicians in the treatment of this complex condition (Fig. 1).

Active substance use disorder should be attended to before the symptoms of ADHD are addressed. Experts often recommend a 3-month period of abstinence before treatment for ADHD may be considered (Brown 2009). However, this may be unrealistic to achieve for patients with significant ADHD symptoms. Some patients with untreated ADHD symptoms may carry the risk of relapse or drop out from the services and find it difficult to engage with other interventions offered. In such cases it is vital to engage patients in an integrated treatment programme and if possible provide an early and aggressive treatment of the ADHD at initial entry into detoxification or rehabilitation programmes (Barkley 2008). Goossensen *et al* (2006) developed and tested



**FIG 1** Treatment algorithm for the management of attention deficit-hyperactivity disorder (ADHD) comorbid with substance use disorder. CBT, cognitive-behavioural therapy; CDAT, community drugs and alcohol team; NRT, nicotine replacement therapy.

an intervention programme for the screening, diagnosis and treatment of ADHD in patients with substance use disorder in two addiction centres in The Netherlands. Treatment consisted of four interventions (education, medication, coaching and peer support groups) and was simultaneously provided and integrated into the treatment of substance use disorder. The programme was well accepted by patients and feasible to implement. In a naturalistic study, Blix and colleagues (2009) evaluated benefits of combined treatment with opioids and central stimulants in a comprehensive treatment facility for substance use disorders. Results were encouraging, with reduction in both opioid misuse and ADHD symptoms and warrant future research to investigate such integrated treatment programmes.

Gray *et al* (2009) provide some practical recommendations specifically in relation to smoking cessation in patients with ADHD and nicotine dependence. The authors recommend stabilisation of ADHD symptoms as the first priority of treatment, since untreated ADHD could lead to greater relapse to smoking. The second step is to encourage patients to quit smoking and once that is established the third step is to initiate smoking cessation. A similar approach may be used in treatment of caffeine dependence in patients with ADHD.

Treatment of ADHD with active substance use disorders should entail effective interagency liaison. Close working with agencies involved (e.g. substance misuse, forensic and police services), family and close friends will ensure better monitoring of illicit drug use, treatment adherence and abstinence from illicit drugs.

Close monitoring is vital and it is imperative to watch for signs of possible misuse, such as missed appointments, and signs of possible diversion, such as repeated requests for higher doses and a pattern of 'lost' prescriptions (Szobot 2008). It is important to exclude risk factors for prescription misuse and diversion. These include individuals with comorbid antisocial personality disorder, strong forensic history and family member or peers with substance use disorder.

For those who have stabilised substance use disorder or merely a history of substance use disorder or recreational substance use and no evidence of ongoing diversion or high-risk situations, extended-release or longer-acting stimulants are recommended. For those with active substance use disorder and/or high risk of diversion, non-stimulants such as atomoxetine and bupropion should be considered. Studies (Stoops 2008; Sofuoglu 2009) determining the effects of atomoxetine on administration of stimulants such

as dextroamphetamine and cocaine support its safety and tolerability when co-administered with stimulants.

Given the lack of robust evidence for pharmacological interventions in patients with ADHD and substance use disorder, clinicians should make an effort to offer their patients a combination of medication and psychotherapeutic interventions. Psychoeducation for patients and caregivers to inform on the condition, natural history and prognosis is an important element to improve recognition and treatment of ADHD with substance use disorder. Structured, adapted psychotherapies (Young 2007) which incorporate motivational enhancement, CBT and/or contingency management to combat substance use disorder can be very useful in treating patients with ADHD and comorbid substance use disorder.

### Future directions

Substance use disorder is a highly prevalent comorbidity in patients with ADHD. Although robust evidence exists for pharmacological management of ADHD, there is dearth of evidence for the management of ADHD with comorbid substance use disorder. More research is required to investigate pharmacological and non-pharmacological treatments of ADHD with comorbid substance use. It is imperative that mental health professionals receive training in assessment and management of ADHD and substance use disorder. Future guidelines should be more explicit with respect to recommendations for this complex, highly prevalent and impairing condition.

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## MCQ answers

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**MCQs**

Select the single best option for each question stem

**1 Which of the following statements is false:**

- a studies in both adults and adolescents have found ADHD to be associated with earlier initiation and higher rates of lifetime substance use
- b substance use can be considered as a form of self-medication for patients with ADHD
- c abstinence may be more difficult for adults with ADHD
- d ADHD predicts the development of alcohol use disorders
- e ADHD greatly elevates risk of substance use and misuse.

**2 Which of the following statements is true:**

- a atomoxetine, a non-stimulant, is a highly specific noradrenergic reuptake inhibitor with high misuse liability
- b caffeine is an effective treatment for ADHD
- c studies demonstrate that stimulants are more effective than non-stimulants in treating ADHD comorbid with substance use disorder
- d bupropion is an effective smoking cessation treatment
- e nicotine is an effective treatment for ADHD.

**3 Which of the following statements is false:**

- a it is imperative to watch for signs of possible misuse when treating patients with ADHD comorbid with substance use disorder
- b at least 1 month of abstinence is useful for accurate and reliable assessment for ADHD symptoms
- c screening instruments for adult ADHD add no benefit in the assessment of ADHD in substance use disorder
- d patients presenting with substance use disorder should be screened for presence of ADHD
- e lisdexamfetamine dimesylate has low misuse liability.

**4 Which of the following statements is true:**

- a treating ADHD pharmacologically with stimulants during an active substance use disorder exacerbates the substance use disorder
- b there is strong evidence that stimulant use in childhood or adolescence increases the risk of developing substance use disorders
- c newer extended-release stimulants and prodrug formulations minimise the risk of misuse and diversion of drugs

- d psychological interventions provide no benefit in treating ADHD comorbid with substance use disorder
- e stimulants have no role in treating ADHD with comorbid substance misuse.

**5 Which of the following statements is false:**

- a therapeutic interventions for ADHD and substance use disorder are multimodal
- b if substance use disorder is active, it should be addressed prior to attending symptoms of ADHD
- c for those with active substance use disorder, and/or high risk of diversion, stimulants should be considered as first-line agents
- d psychoeducation for patients and caregivers is an important element to improve recognition and treatment of ADHD with substance use disorder
- e substance use in ADHD may be considered as a form of self-medication.