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# Alcohol, drugs, and attention-deficit/hyperactivity disorder: a model for the study of addictions in youth

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## Abstract

There has been increasing interest in the developmental origins of substance use disorders (SUDs) in children and adolescents. Because of its early onset, high prevalence and known risk for SUD, attention deficit hyperactivity disorder (ADHD) is a model developmental disorder to evaluate in context to SUDs. A selected review of the literature was undertaken examining ADHD as an antecedent disorder to subsequent SUD. ADHD and its co-occurring comorbid psychopathology increase the risk for cigarette smoking and SUD and is associated with greater SUD severity and chronicity. The treatment of ADHD appears to decrease the risk for cigarette smoking and SUD. ADHD is an important antecedent disorder in children and adolescents worthy of further targeted preventive efforts to diminish the risk for cigarette smoking and SUD.

### Keywords

alcohol abuse, ADHD, drugs

## Introduction

Juvenile-onset alcohol or drug abuse and dependence (termed substance use disorder [SUD]) represents a major clinical and public health concern. Recent data indicate that 9% of Americans, aged 12 or older, have a SUD and that some children are already abusing drugs by the age of 12 years (Johnston *et al.*, 2004). Despite trends showing a decline in SUD over the past year (Johnston *et al.*, 2004), the amount of SUD among adolescents is still high and is in need of further attention. In addition to the vast cost to the family and society, SUD has a negative impact on the educational and emotional development of the young, and ultimately their outcome as adults (Kandel and Logan, 1984).

Given that data indicate that a majority of SUDs originate in adolescence (Irwin *et al.*, 1990; Babor *et al.*; 1992, Johnston *et al.*, 2004), SUD is increasingly being conceptualized as a developmental disorder. It is reasonable to consider that the earlier in the course of illness an intervention is initiated, the more likely a successful outcome. Hence, the identification and treatment of antecedent disorders to subsequent SUD is of great importance.

Among of the most studied antecedent disorders to SUD is attention deficit hyperactivity disorder (ADHD). ADHD is a highly prevalent, morbid and persistent disorder of childhood-onset that affects 6–9% of youth and 4% of adults worldwide (Faraone *et al.*, 2003). It is well known to be associated with neuropsychological impairment, academic underachievement, low self-esteem and high levels of psychiatric comorbidity that have independently been linked with SUD (Wilens *et al.*, 2002). Of particular interest is that ADHD onsets in early childhood many years prior to the onset of SUD. In this article we review a selected body of work, investigating the relationship between ADHD and SUD conducted over the last 20 years.

### *Is ADHD over-represented in subjects with SUD?*

An over-representation of ADHD has been consistently observed in studies of adolescents and adults with SUD. Between 25 and 50% of adolescents with SUD have been reported to have ADHD (DeMilio, 1989; Hovens *et al.*, 1994). For example, the large, multisite, Cannabis Youth Treatment study reported that ADHD was the second most common comorbidity associated with cannabis abuse or dependence (Dennis *et al.*, 2002) – equally distributed between males and females. In studies of adolescents identified with SUD, mood and conduct disorder (CD) were frequently observed in ADHD youth with SUD (DeMilio 1989; Hovens *et al.*, 1994; Wilens *et al.*, 1997a).

Similarly, reviews of adult studies (Levin and Evans, 2001; Wilens, 2004a) indicate that the overlap between SUD and ADHD is larger than expected by chance. Studies of subjects with alcohol and drug use disorders indicate that from 15 to 25% of adults referred for SUD have ADHD (Carroll and Rounsaville, 1993; Levin *et al.*, 1998; Schubiner *et al.*, 2000; Wilens, 2004a).

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## *Are cigarette use and SUD over-represented in ADHD?*

Retrospective and prospective studies of ADHD indicate a twofold increased risk for cigarette smoking in referred and non-referred ADHD adolescents compared to their non-ADHD peers (Milberger *et al.*, 1997). The higher risk of cigarette smoking in ADHD is observed equally in both genders. Significant differences in cigarette smoking persist in ADHD with a higher frequency in young adult years even outside of conduct disorder (Lambert and Hartsough, 1998; Wilens, 2004b).

While the link with cigarette smoking has been established, even more data are surfacing on the risk of ADHD for SUD. Prospective studies of ADHD children into adolescence and adulthood have provided evidence that ADHD is a risk factor for SUD (Molina and Pelham, 2003; Wilens, 2004b). For instance, Molina and Pelham (2003) reported that the persistence of ADHD, disruptive disorders and attentional dysfunction in childhood, predicted SUD in adolescence. A review of the literature indicates consistently higher rates of SUD in ADHD probands as adults relative to controls – and that psychiatric comorbidity increases this risk (Weiss *et al.*, 1985b; Lambert, 1988; Mannuzza *et al.*, 1989; Barkley *et al.*, 1990a; Biederman *et al.*, 1997; Molina and Pelham, 2003).

## *Conduct disorder, mood, ADHD, and SUD*

Because ADHD is frequently comorbid with mood and CD, understanding the components risk in context to ADHD is an essential aspect of disentangling SUD issues in juveniles. Numerous studies have demonstrated that childhood CD (and the adult antisocial counterpart) is one of the most robust and predictable risks in foretelling early onset SUD in adolescence and young adults (Robins, 1966; Brook *et al.*, 1996; Crowley *et al.*, 1998). Within ADHD, our data indicate that adolescents with ADHD and CD start smoking earlier and at a higher frequency than ADHD without CD or non-ADHD controls (Milberger *et al.*, 1997). Our studies of untreated ADHD and control adults found the highest risk for SUD among subjects with CD and/or antisocial disorders (Biederman *et al.*, 1995; Wilens *et al.*, 1997b). These findings in adults were consistent with a number of prospective studies of grown-up ADHD children in which a higher risk for SUD was predicted specifically by comorbid CD and/or current antisocial disorder (Satterfield *et al.*, 1982; Weiss *et al.*, 1985a; Mannuzza *et al.*, 1989; Barkley *et al.*, 1990b; Biederman *et al.*, 1997).

Investigations have highlighted the need for attention to mood symptoms in CD, particularly in SUD (Riggs *et al.*, 1995; Crowley *et al.*, 1998). Approximately 20% of CD substance abusing boys have a depressive disorder not secondary to the SUD (Riggs *et al.*, 1995) and these adolescents had high rates of other psychopathology, and earlier onset CD. Open antidepressant treatment of youth with mood disorders and CD have shown to reduce both mood and CD symptoms (Riggs *et al.*, 1997) – suggesting that depression may be an important treatable comorbid condition in CD adolescents with SUD.

Similar findings are emerging for bipolar disorder (BPD). A growing literature shows a bidirectional overlap between BPD and cigarette smoking and SUD in adolescence (West *et al.*, 1996; Biederman *et al.*, 1997; Wilens *et al.*, 1997a; Wilens *et al.*, 1999; Wilens *et al.*, in press). For example, prospective studies of children show that early-onset BPD highly comorbid with ADHD is a risk for SUD independently of ADHD (Biederman *et al.*, 1997; Wilens *et al.*, 2005).

The available literature is consistent in showing that the onset of ADHD, CD and BPD precedes the onset of SUD in the vast majority of children. Similar findings had been reported in studies that examined the temporal sequence of mood disorders in samples of adolescents with SUD (Bukstein *et al.*, 1992). Taken together, these findings indicate that psychopathology frequently precedes SUD in youth (Brook *et al.*, 1998) and support the notion that psychopathology is not merely secondary to SUD in the majority of such adolescents (Bukstein *et al.*, 1992).

## *Does gender moderate the risk for SUD in ADHD?*

The effect of gender in the risk for SUD is an area of ongoing scientific inquiry (Faraone *et al.*, 2000; Hinshaw *et al.*, 2002). Both epidemiological and clinical samples suggest that ADHD girls have a higher risk for smoking and substance use by early adolescence relative to boys (Biederman *et al.*, 1999; Disney *et al.*, 1999). For instance, Disney *et al.* (1999) as part of the Minnesota Twin project, reported trends to higher rates of SUD within the past month in 17 year old girls versus boys with ADHD (any substance use: 73% vs 44%; SUD: 29% vs 14%, respectively). Likewise, our studies show a higher age-corrected risk for SUD in ADHD girls compared to similarly ascertained boys (Biederman *et al.*, 1991; Biederman *et al.*, 1999). This finding is particularly notable considering that ADHD girls had one third the rate of CD than that observed in boys and CD is a known risk factor for SUD (Robins, 1966). These findings suggest that girls with ADHD develop SUD approximately 2 years earlier than boys with ADHD (Milberger *et al.*, 1997; Disney *et al.*, 1999). While the reason for this discrepancy remains unclear, it may be the earlier socialization of girls relative to boys, placing them with peers who use cigarettes and other substances, accounting for these findings.

## *Does ADHD influence the pathways to SUD?*

It has been hypothesized that substances that are legal for adults such as alcohol and cigarettes tend to increase the risk for using illicit drugs (gateway hypothesis) (Kandel and Logan, 1984). This potential pathway to drug use is of particular significance given that nationwide surveys of high school seniors reveal that one third of students were stable smokers and one third had been drunk within the past month. The transition from licit substance use such as cigarette smoking to illicit substance abuse is an area of intrigue and may be of particular interest in ADHD. Adolescents with ADHD are at heightened risk for the development of cigarette smoking compared to matched adolescents without ADHD (Milberger *et al.*, 1997; Wilens, 2004b). In fact, very recent data from our group show that cigarette smoking in ADHD is twice as frequent as in controls and predicts subsequent SUD (Biederman *et al.*, 2006).

Several ideas have been proposed as to why cigarette smoking

in ADHD is predictive of SUD. Exposure to peers who are smoking cigarettes and using other licit (alcohol) and illicit substances is compelling in explaining the link (Kandel and Logan, 1984). Alternatively, preclinical investigators (Fung and Lau, 1989) hypothesized that early exposure to nicotine may result in neuronal sensitization and kindling, predisposing to later behaviours linked to SUD.

From a preventive standpoint, reducing the manifest psychiatric symptoms, such as in ADHD, may result in a decrease in cigarette use risk – as has been shown recently in a prospective trial of up to 6 years indicating that stimulant pharmacotherapy of ADHD protects against the onset of cigarette smoking significantly in adolescents (Monuteaux *et al.*, 2004). Of interest, nicotine and nicotinic agonists have been shown to be effective in treating ADHD (Conners *et al.*, 1996).

Findings also indicate that ADHD accelerates the transition from substance *abuse* to *dependence* (Biederman *et al.*, 1998). Also, ADHD increases the risk for a drug use disorder, in individuals with alcohol abuse or dependence (Biederman *et al.*, 1998). ADHD also affects remission from SUD. In a study of 130 referred adults with ADHD plus SUD and 71 non-ADHD adults with SUD, the median time to SUD remission was more than twice as long in ADHD than in control subjects (144 versus 60 months, respectively) (Wilens *et al.*, 1998). Studies in ADHD adults suggest that the persistence of ADHD results in continued misuse and abuse of substances after dependence, a longer duration of SUD and a lower rate of remission (Biederman *et al.*, 1998; Wilens *et al.*, 1998). Similarly, treatment seeking substance abusing adults with ADHD have been shown to have a more chronic and severe form of SUD, along with more difficulty in recovery from cigarette dependence and SUD (Carroll and Rounsaville, 1993; Pomerleau *et al.*, 1995; Schubiner *et al.*, 2000). Taken together, these findings indicate that ADHD influences the initiation, transitions and recovery from SUD.

## *Do ADHD individuals self-medicate with drugs and alcohol?*

As articulated by Khantzian (1997), substances of abuse may be appealing to individuals based on the main action or effect of the drug, the personality organization or characteristics of that individual, and his or her inner states of psychological suffering or disharmony. These traits are genetically and developmentally influenced and by themselves are a risk for SUD (Khantzian, 1997). The self-medication hypothesis is plausible in ADHD considering that the disorder is chronic and often associated with self-regulatory deficits, comorbid affective symptoms, demoralization and failure, factors frequently associated with SUD in adolescents (Shedler and Block, 1990). Moreover, the accompanying poor judgement, and impulsivity associated with ADHD may be particularly noxious for the development of SUD considering that adolescence is a high risk time for the development of SUD.

Evidence exists for a subgroup of ADHD individuals to be self-medicating. Mannuzza *et al.* (1989) suggested a developmental progression in ADHD characterized by demoralization, failure, substance misuse leading to delinquency and SUD. Yet, while ADHD individuals appear to use drugs over alcohol compared to their non-ADHD peers (Biederman *et al.*, 1995; Biederman *et al.*, 1997; Molina and Pelham, 2003), the choice of a specific drug of abuse (e.g. cocaine over marijuana) has not been shown for ADHD individuals with SUD (Biederman *et al.*, 1995; Biederman *et al.*, 1997). Both cross sectional (Horner and Scheibe, 1997) and longitudinal studies (Wilens, 2004b) in adolescents and young adults indicates that compared to controls, ADHD individuals frequently use substances of abuse to attenuate their mood, restlessness, and to assist with sleep.

## *Do ADHD and SUD share familial underpinnings?*

Family studies are highly informative to help examine the nature of the association between two co-occurring disorders. A familial association between ADHD and SUD has been documented in the first- and second-degree family members of children with ADHD (Morrison and Stewart, 1971; Cantwell, 1972; Faraone and Doyle, 2001). Controlled family-genetic studies of ADHD have supported the hypothesis of independent transmission of SUD and ADHD (Faraone and Doyle, 2001).

Family, twin, and adoption studies indicate that both genes and environment have etiologic roles in the development of SUD (Cloninger, 1987; Hopfer *et al.*, 2003) and of ADHD (Faraone and Doyle, 2001). In adolescents, moderate heritability has been reported for nicotine dependence and for SUD (Hopfer *et al.*, 2003). For instance, higher heritability has been noted in older adolescents relative to younger adolescents (Koopmans *et al.*, 1999; Hopfer *et al.*, 2003). It has been suggested that the risk for SUD is moderated through variables such as comorbid psychopathology (e.g. CD, bipolar disorder), temperamental or personality traits (e.g. disinhibited temperament). For example, disinhibited youth have been shown to be at increased risk for SUD (Tarter *et al.*, 2003) and studies suggest that this phenotype appears to be linked to the genetic risk for SUD (Hopfer *et al.*, 2003).

Parental SUD has also been associated with higher than expected rates of SUD, ADHD and other psychopathological conditions in their high risk children (Earls *et al.*, 1988; Nunes *et al.*, 1998). An elevated risk of ADHD in school aged children of SUD parents has been consistently noted in clinical and community based studies (Zucker and Noll, 1987; Earls *et al.*, 1988; Nunes *et al.*, 1998). It is noteworthy that the heightened risk for ADHD in the offspring of SUD parents appears to be observed already in preschoolers aged 3 to 5 years (Zucker and Noll, 1987). While parental SUD increases the risk for ADHD in the offspring, an additive risk for ADHD in offspring has been observed in those parents with ADHD plus SUD (Wilens *et al.*, 2005).

Although studies have shown that genes account for some of the familial transmission of adolescent SUD, they also implicate environmental factors (Hopfer *et al.*, 2003). It is likely that many environmental risk factors combine to elevate or diminish the risk for SUD in youth at specific times. For example, younger adolescents may be more vulnerable to environmental risk factors compared to older adolescents (Hopfer *et al.*, 2003) and both sibling and peer adversely influence the vulnerable adolescent's use of substances (Legrand *et al.*, 1999). Although many details about

the etiology of SUD in adolescence remain unknown, the literature is consistent with the hypothesis that early onset SUD may develop when a genetic predisposition is triggered by environmental events.

One manner by which the offspring of parents with SUD may be at risk for ADHD is through gestational exposure to substances – particularly cigarette smoking and alcohol. For example, children with fetal alcohol syndrome tend to be at risk for persistent ADHD (Steinhausen *et al.*, 1993). More recent work suggests an increased risk for ADHD associated with maternal smoking (Milberger *et al.*, 1996; Weissman *et al.*, 1999; Mick *et al.*, 2002).

Results from recent animal studies provide plausible biological mechanisms for the effects of prenatal exposure to alcohol and cigarettes. Roy *et al.* (1998) found increased incidence of apoptotic cells in the hindbrain, forebrain and midbrain of rat embryos exposed to nicotine that were insufficient to cause general dysmorphogensis (Roy *et al.*, 1998; Ikonomidou *et al.*, 2000). Thus, levels of exposure to nicotine that do not affect the viability of the fetus may result in disruption of normal brain development leading to ADHD and other psychopathology that then predisposes to SUD.

## *Does exposure to parental SUD increase SUD risk in ADHD children?*

Children may also be at increased risk by being exposed behaviourally to a parent's SUD. Data indicate that in ADHD, exposure to parental SUD, especially during adolescence, predicts SUD in the offspring (Biederman *et al.*, 2000). The deleterious influence of exposure to parental SUD is consistent with social learning theories of substance use, especially parenting styles and parental modeling, which has been shown to be an important risk factor in the substance use of young people (Bailey, 1989). Exposure to a laissez-faire type of parenting, with poor and inconsistent family management practices, has been shown to be a major risk factor for SUD in adolescence (Hawkins *et al.*, 1992).

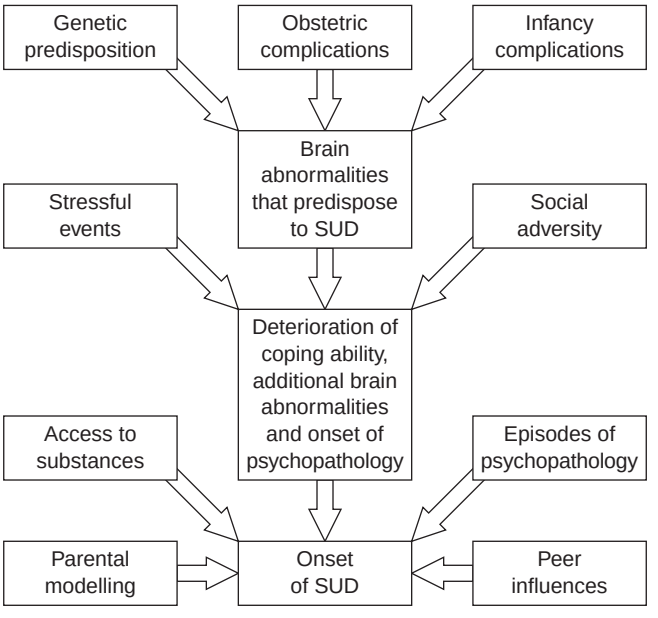


**Figure 1** Hypothetical developmental sequence of the etioloy of substance use disorders

## *Are there temperamental risk factors for SUD in ADHD?*

One proposed genetically mediated personality trait that has been linked to both SUD and ADHD is novelty seeking and to a lesser extent harm avoidance and reward dependence (Cloninger, 1987). For example, substance use is elevated in adolescents with high novelty seeking, low harm avoidance and low reward dependence (Wills *et al.*, 1994) and, high novelty seeking and low harm avoidance measured at ages 6 and 10 years predicts early onset of SUD in adolescence (Masse and Tremblay, 1997). Novelty seekers are impulsive, exploratory, excitable and quick tempered – well-known features of ADHD. Further evidence for links among ADHD, novelty seeking and SUD is found in molecular genetic studies. In addition to its reported association with novelty seeking and ADHD, the DRD4 gene has also been implicated in SUD (Kotler *et al.*, 1997). Preclinical studies indicate that novelty seeking animals not only are predisposed to develop amphetamine self-administration in experimental paradigms but have high levels of dopamine activity in the nucleus accumbens (Dellu *et al.*, 1996).

It is well known that adolescence is a critical developmental period for the emergence of SUD (Kandel and Logan, 1984). By nature of availability, peer influences and other factors, we expect factors that trigger the genetic liability to SUD to be more potent during adolescence than during childhood. Findings on the timing of risk factors suggest that models of the etiology of SUD must consider the developmental sequence of gene expression from conception through birth and from childhood through adulthood. In Fig. 1, we apply this model to SUD, but extend it by adding some of the many risk factors relevant to ADHD. The top of the Figure defines the putative starting point of SUD: the set of disease predisposing genes that are determined at conception. This predisposition in conjunction with prenatal events and infant complications may lead to brain abnormalities that predispose to ADHD, SUD, or the combination.

The next step in the pathophysiologic chain of events occurs when the brain is exposed to environmental events in childhood, prior to adolescence. These include specific stressful life events such as child abuse and chronic exposures to social adversity such as poverty, demoralization and lack of parental supervision. These could lead to a deterioration of coping ability, additional brain abnormalities and the further onset of psychopathology. Fig. 1 also shows that, during adolescence, the effects of access to substances, parental modeling, episodes of psychopathology and peer influences can lead to the onset of SUD in adolescence.

## *Is there a common neurobiological substrate for ADHD and SUD?*

Neuropsychological deficits have been documented consistently in studies of both adolescents and adults with ADHD and those with SUD. These deficits are associated with impaired performance on tasks assessing vigilance, motoric speed, response inhibition, verbal learning and working memory (Epstein *et al.*, 1997). Prominent executive dysfunction have been reported in ADHD including deficits in organization, planning and complex problem solving (Barkley, 1997; Seidman *et al.*, 1997). Similarly, a growing literature highlights neuropsychological dysfunction and learning disabilities as a risk factor for SUD (Beitchman *et al.*, 1999; Tapert *et al.*, 2002). For example, in a longitudinal study of 66 high risk adolescents, Tapert *et al.* (2002) reported that executive function and attentional deficits on neuropsychological testing predicted an increased risk for SUD in young adulthood. While neuropsychological testing is not used clinically to diagnose ADHD or SUD, such testing aids in identifying learning disabilities, subaverage intelligence and specific information processing deficits in individuals with ADHD and SUD, deficits that may place children and adolescents at risk for SUD (Beitchman *et al.*, 1999).

As recently reviewed (Faraone and Biederman, 2002; Chambers *et al.*, 2003), current thinking suggests that a network of interrelated brain areas may overlap in explaining the attentional–executive impairments of SUD and ADHD. The cingulate cortex plays a role in motivational aspects of attention and in response selection and inhibition. A system mainly involving the right prefrontal and parietal cortex is activated during sustained and directed attention across sensory modalities (Faraone and Biederman, 2002). Working memory deficits implicate a distributed network including the anterior hippocampus, ventral anterior and dorsolateral thalamus, anterior cingulate, parietal cortex and dorsolateral prefrontal cortex (Faraone and Biederman, 2002).

Substances of abuse may alter adolescent neurodevelopment particularly in regards to motivation and impulsivity (for review see Chambers *et al.*, 2003). Many drugs of abuse affect both prefrontal and subcortical areas resulting in alterations in dopaminergic and glutaminergic systems that may accentuate adolescent impulsivity and novelty seeking (Volkow *et al.*, 2004). Maturation occurring during adolescence on prefrontal cortex (processing, executive functions, inhibitions), striatum/nucleus accumbens (signal enhancement and refinement) and geographically juxtaposed hypocampal and amygdala (memory, emotion, motivation) may make this age group particularly vulnerable neurobiologically for the acute and long-term consequences of substances of abuse (Chambers *et al.*, 2003; Kalivas, 2003). For instance, important connectivity between limbic regions such as amygdala and the striatum and nucleus accumbens may be influenced by substances of abuse as well as by mood and anxiety states. Repeated use of substances may influence adversely the nucleus accumbens and striatal interactions with the prefrontal cortex (and vice versa) (Chambers *et al.*, 2003; Kalivas, 2003). These events may also facilitate aberrant neuroplasticity among nucleus accumbens neurons determining cortical maturation (Masterman and Cummings, 1997). In turn, important motivational capacity may be affected along with novelty coding dopamine activity resetting the 'motivation arcs' – thus furthering the addictive potential of drugs of abuse (Chambers *et al.*, 2003; Kalivas, 2003). It is no coincidence that many of the postulated brain regions involved in addictive behaviours overlap with those implicated in ADHD and comorbid mood and anxiety states.

## *What is the approach for treating adolescents with ADHD and SUD.*

Cigarette and substance use in adolescents should lead to aggressive management efforts. Evaluation of the adolescent with active SUD includes determining symptoms of ADHD, other psychopathology, cognitive deficits, family and peer constitution, medical problems and psychosocial functioning. Structured psychiatric interviews are invaluable aids for the systematic diagnostic assessments of this age group. Although the treatment needs of individuals with SUD and ADHD need to be considered simultaneously, SUD should be addressed initially (Riggs, 1998). Controlled data indicate, that when treating only ADHD in adolescents with SUD, no changes in SUD and only meager improvement in ADHD can be expected (Riggs *et al.*, 2004). In parallel to addiction treatment, adolescents with SUD and ADHD (comorbidity) require intervention(s) for the ADHD, and other comorbid psychiatric disorders (Riggs, 1998). Despite an increased abuse liability with the stimulants (Drug Enforcement Administration, 1995), controlled studies of amphetamine and methylphenidate as replacement agonists in active SUD (generally cocaine or amphetamine abusers) with and without ADHD have shown some benefit for the SUD and have not been associated with worsening of SUD, craving or drug–drug interactions (Schubiner *et al.*, 2002; Grabowski *et al.*, 2004).

Cognitive-behavioural therapy (CBT) is one therapeutic intervention useful in SUD (for review see Waldron and Kaminer, 2004) and ADHD ± comorbidity (McDermott and Wilens, 2000). Studies of individual and group CBT support the efficacy for SUD reduction assessed both at the endpoint and up to 6 months after treatment termination in both motivated and unmotivated adolescents (Waldron and Kaminer, 2004).

There are very limited data on direct pharmacotherapy for SUD in adolescents. Hypothetically, aggressive treatment of SUD in adolescents may translate into an improved response compared to adults given the proximity of treatment relative to the onset of the SUD. Only case reports of agents that are aversive in nature (e.g. disulfiram) exist (Kaminer, 1995) and agents of substitution remain essentially untested in adolescents. Ondansetron, a serotonin antagonist, is of interest in adolescents, given that it significantly reduced alcohol consumption only in adults with early (childhood)-onset SUD (Johnson *et al.*, 2000). Given that agents may have more efficacy in pediatric groups (Johnson *et al.*, 2000) by nature of the subtype with the more acute recent onset of SUD, and hence less chemical and neuroplastic changes associated with chronic SUD (Chambers *et al.*, 2003), adolescents are an ideal group to evaluate in terms of agents directed specifically at the underlying SUD.

### *Does the treatment of ADHD attenuate the risk for SUD?*

The critical influence of long-term treatment of psychopathology on later cigarette use and SUD remains hampered by methodological issues such as the inability to disentangle positive or deleterious effects of treatment from the severity of the underlying condition. Whereas concerns of the abuse liability and potential kindling of specific types of abuse (i.e. cocaine) secondary to stimulant treatment of ADHD children have been raised (Drug Enforcement Administration, 1995), the preponderance of clinical data (Wilens *et al.*, 2003) do not support such a contention. For example, a meta-analytic review of the literature revealed a twofold reduction in risk for SUD in youth associated with treatment with stimulants compared to no pharmacotherapy for ADHD (Wilens *et al.*, 2003). Hence, as a model, the treatment of ADHD appears to be associated with a reduction in the risk for SUD and may serve as a role for other mood and disruptive disorders.

Diversion and misuse of stimulants remains an issue, generally through oral and intranasal routes by non-ADHD individuals for their performance enhancement and euphoric properties (Drug Enforcement Administration, 1995). Consistent with others (Poulin, 2001), we recently found that 11% of young adults (age 21 years) with ADHD had sold their stimulants (Wilens, 2004b). Of interest, those with ADHD who diverted or misused their stimulants all had SUD and/or CD and only immediate-release, not extended-release, stimulants were misused or diverted. Not surprisingly, intranasal and intravenous administration of poorly bioavailable compounds such as MPH have very different pharmacokinetic and pharmacodynamic effects compared to oral administration of these agents (Volkow *et al.*, 1998; Stoops *et al.*, 2003) explaining the exploitation of these agents for recreational use by non-oral routes.

## Summary

In summary, important developmentally based findings relative to SUD risk surfaces when characterizing the nature of SUD and ADHD. The aggregate data supports that ADHD is a common childhood disorder that onsets early in life prior to SUD and that persistent ADHD is associated with subsequent SUD. Neuropsychological and neurobiological substrates are operant and may account for part of the link between ADHD and SUD. Limitations in the literature punctuate a number of areas in need of further study. The course of SUD in ADHD, and genetic predictors of a SUD phenotype need further investigation. The mechanism(s) underlying SUD in ADHD needs to be further explored with a target of altering identified variables to attenuate the ultimate risk for SUD. Novel treatments and the sequence of interventions for substance abusing adolescents with ADHD need be established. Given the common occurrence and major morbidity related to SUD and ADHD (and related psychopathology), aggressive early identification and treatment at a premorbid stage need be considered.

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## Declaration of interest

Dr Wilens is Director of Substance Abuse Services, Clinical Research Program in Pediatric Psychopharmacology, Massachusetts General Hospital, and Associate Professor of Psychiatry, Harvard Medical School. Dr Biederman is Chief of the Clinical Research Program in Pediatric Psychopharmacology, Massachusetts General Hospital, and Professor of Psychiatry, Harvard Medical School.

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