ADDICTIVE DISORDERS & THEIR TREATMENT

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Addressing Dual Diagnosis Patients Suffering from Attention-Deficit Hyperactivity Disorders and Comorbid Substance Use Disorders: A Review of Treatment Considerations

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Abstract

Objective:
To provide an updated, thorough, and critical review of the current status of the pharmacological and psychosocial treatments of patients with attention-deficit hyperactivity disorder (ADHD) and a comorbid substance use disorder (SUD).

Methods:
Comprehensive and systematic search of relevant databases (Medline, PubMed, Embase, and the Cochrane Library of systematic reviews and clinical trials) was carried out until January 31, 2012.

Results:
Treatment of patients with ADHD and a comorbid SUD is based on a multimodal and integrated approach, requiring the adequate management of the comorbid disorders, with psychosocial and pharmacological treatments. Regarding the pharmacotherapies for ADHD, prescription psychostimulants, particularly methylphenidate and atomoxetine, have all been assessed in dually diagnosed patients, for treating the symptoms of ADHD or for managing the comorbid SUD. Overall, medications are safe, well tolerated, and provide short-term and long-term benefits in patients with ADHD and comorbid SUD.

Conclusions:
Studies assessing the efficacy of pharmacotherapies for ADHD have shown that they are equally efficacious and well tolerated, generally in combination with psychological interventions, in patients with a comorbid SUD. In addition, psychostimulant treatment of children with ADHD appears to have a protective effect on the subsequent risk for SUD.

Key Words: dual disorders, ADHD, substance use disorders, treatment, addiction

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Attention-deficit hyperactivity disorder (ADHD) is a common, complex, and multifactorial disorder characterized by developmentally inappropriate levels of inattention, hyperactivity, and/or impulsivity.[1] Over the recent decades, ADHD has been recognized not only as the most frequent neurobiological disorder in childhood, but also as a chronic neurodevelopmental disorder. Symptoms persist into adulthood in approximately 60% of the patients, and at least 30% of children diagnosed of ADHD continue presenting the full syndrome even when adults.[2,3] It is estimated that the prevalence of ADHD in general adult population is 3% to 5%.[4,5]

Comorbid psychiatric disorders are very common in individuals with a diagnosis of ADHD. Conduct disorders, oppositional defiant disorders, learning impairments, anxiety disorders, and mood disorders are the most frequent psychiatric comorbidities in children or adolescents with ADHD.[6] Mood disorders are also often present in adult patients with ADHD, with an estimated risk for developing major depressive disorder 2.7 times higher than in healthy controls.[4] Similarly, several studies have suggested that at least 20% of patients with bipolar disorder have a comorbid ADHD.[7,8] Other psychiatric disorders frequently seen in adult individuals with ADHD include personality disorders,[9–11] anxiety disorders,[4,12] or eating disorders.[13]

There is a robust overlap between ADHD and substance use disorders (SUD), with important implications in daily clinical practice, in research, and in public health.[14] Multiple studies,[4–19] including several systematic reviews with meta-analyses,[20,21] have evidenced

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that ADHD is an independent risk factor for developing nicotine, alcohol, or other substance abuse or dependence, although the coexistence of a conduct disorder during childhood increases the risk, and the latter is the strongest predictor of differences in patterns of drug use severity.[22] Prevalence of SUD is high among patients with ADHD. It is estimated that the prevalence is approximately double than in the general population.[4,15,17,23,24] Conversely, individuals with substance abuse or dependence have higher rates than that expected of a comorbid ADHD. The majority of studies coincide that 15% to 25% of adults with an addictive disorder have a comorbid ADHD,[19,25–30] rates much higher than observed in individuals of same age from general population. Patients with ADHD and a comorbid SUD have lower retention rates in addiction treatment programs, as well as lower remission rates and more chronicity of the SUD.[31]

In the present report, it is aimed to provide an updated and thorough review of the current status of the pharmacological and psychosocial treatments of patients with ADHD and a comorbid SUD.

METHODS

A comprehensive and systematic search of relevant databases (Medline, PubMed, Embase, and the Cochrane Library of systematic reviews and clinical trials) was conducted to identify all articles published until January 31, 2012. Search terms included: ''ADHD,'' ''substance use disorders,'' ''dual diagnosis,'' ''comorbid disorders,'' ''methylphenidate,'' ''atomoxetine,'' ''clonidine,'' ''guanfacine,'' ''amphetamine,'' and ''lisdexamfetamine,'' together with the PubMed clinical queries algorithms for etiology, prognosis, treatment, and systematic reviews. In addition, reference lists were scrutinized to identify and retrieve further reports and studies on these topics from additional sources and scientific databases. There were no restrictions on the identification or inclusion of studies in terms of date of publication, language, publication status, and design type. However, abstracts of presentations to specialist meetings and conferences were not included.

Treatment of Patients With ADHD and Comorbid SUD

The treatment of patients with ADHD and a comorbid SUD is based on a multimodal and integrated approach.[32,33] Given the chronic impairment associated with ADHD across multiple domains of functioning, multimodal interventions that combine the medications for the dual disorders with specific psychological interventions, therefore comprising psychoeducation, pharmacotherapy, coaching, and/or cognitive behavioral therapy (CBT) are not only necessary, but well-recognized treatments of choice for individuals with ADHD, with or without another comorbid mental illness.[32–34] The specific strategies are determined by the severity of the symptoms of both disorders and the problems experienced by the patient. However, it is important to adequately manage the SUD for the better management of the symptoms of ADHD.

Psychological Interventions

Psychotherapeutic and psychosocial interventions are useful and effective strategies for treating patients with ADHD, particularly in combination with medications, to improve outcome,[35,36] and for managing residual symptoms.[32,37,38] They are also indicated for patients with poor tolerability and compliance to pharmacological treatments, and for patients with comorbid psychiatric disorders.[3,34,38]

A wide variety of psychological and psychosocial interventions have been used to manage the symptoms and problems experienced by patients diagnosed with ADHD, including psychoeducation, that is often a key element, particularly in the initial stages of treatment,[32,34,35] coaching, or social skills training. CBT is the nonpharmacological treatment with the highest level of evidence for treating patients with a diagnosis of ADHD of any age, and for those with comorbid disorders, including those patients with comorbid SUD.[33,37,39,40] There are, however, few studies that have systematically evaluated

ADDICTIVE DISORDERS & THEIR TREATMENT
Volume 12, Number 4
December 2013

the efficacy of psychological treatments in adult patients with a comorbid SUD.

Pharmacological Treatment of ADHD in Patients With Dual Disorders

Since the initial reports published in 1937 showing the efficacy of benzedrine, a racemic mixture of L-amphetamine and D-amphetamine, for treating hyperactive children with attentional problems,[41] psychostimulants have been widely used and are still considered first-line treatments for patients with ADHD.[32,33,42] Psychostimulant medications include immediate, intermediate, and long-acting formulations of methylphenidate and amphetamine derivatives.

Originally developed as an antidepressant, atomoxetine was the first nonstimulant medication approved for the treatment of ADHD. Atomoxetine has a high affinity and selectivity for the noradrenaline transporters,[43] but little or no affinity for various neurotransmitter receptors.[44] Because of its ability to inhibit presynaptic noradrenaline reuptake, it increases extracellular noradrenaline and noradrenaline transmission in areas with high distribution of noradrenergic neurons, including the prefrontal cortex and subcortical areas, regions that are significantly compromised in ADHD.[45] Guanfacine HCl, an α_{2A}-adrenergic agonist, has been recently approved in some countries in its extended-release (ER) formulation for treating ADHD in children and adolescents 6 to 17 years of age.[46] Guanfacine enhances the function of the prefrontal cortex, by stimulating postsynaptic α2-receptors.[47] In addition, a variety of medications have been evaluated in research and are commonly used in clinical practice off-label for treating patients with ADHD, including venlafaxine,[48] reboxetine,[49] duloxetine,[50] agomelatine,[51] and particularly bupropion[52] and modafinil.[53]

Although pharmacological treatments constitute the single most efficacious treatment strategy for children, adolescents, and adults with ADHD,[32,33] and despite the strong evidence of the high efficacy of pharmacotherapies used for ADHD compared to other medications for other psychiatric disorders, approximately 20% of patients fail to respond to medication.

Stimulant Medications in the Treatment of Patients With ADHD and Comorbid SUD

Case series reports[54] and open-label studies[55–57] provided initial evidence of the potential beneficial effects and the good tolerability of psychostimulant medications for patients with a diagnosis of ADHD and a comorbid SUD (Table 1). On the basis of these promising data, several double-blind randomized placebo-controlled trials have assessed the efficacy of psychostimulants, particularly methylphenidate for treating dually diagnosed ADHD patients, both in samples of adolescents[58,59] and adults[60–65] (Table 1). In the first of these studies, 48 adult patients with ADHD and comorbid cocaine dependence who were attending weekly therapy sessions participated in a 12-week double-blind trial.[64] Compared with placebo, treatment with methylphenidate (at a maximum daily dose of 90 mg) was well tolerated, and associated with a significant improvement in symptoms of ADHD, although there were no group differences in self-reported cocaine use, urinalysis results, or cocaine craving.

A subsequent study assessed the efficacy of low-dose methylphenidate (at a maximum daily dose of 45 mg) in 25 inpatients with a comorbid diagnosis of ADHD and various SUD admitted at an addiction treatment facility.[60] There was a significant reduction in ADHD symptoms in the first week, but no statistically significant group differences. Similarly, a 12-week trial comparing sustained-release (SR) methylphenidate, SR-bupropion, or placebo in 98 methadone-maintained patients with comorbid ADHD, who were also receiving weekly individual CBT reported that although there was no evidence of misuse of medication or worsening of cocaine use among those randomized to the active medications and there was a reduction in ADHD symptoms in all the 3 groups, taken together, SR-methylphenidate or SR-bupropion did not provide a clear advantage over placebo in reducing ADHD symptoms or additional cocaine use in methadone-maintained patients.[62] In addition, there

were no significant differences in retention rates or in treatment outcomes between methylphenidate and placebo in another study with 106 patients diagnosed of ADHD and comorbid cocaine dependence, who were also receiving weekly CBT, although those patients showing a reduction of ADHD symptoms taking methylphenidate were significantly more likely to show a reduction in cocaine use than those taking placebo, as evidenced in urine toxicological analysis.[63] More recently, the utility of osmotic release oral system (OROS) methylphenidate (OROS-MPH) was evaluated in a 12-week double-blind study in 24 adult patients with a comorbid diagnosis of ADHD and amphetamine dependence.[61] Compared with placebo, OROS-MPH had no significant effect on craving for amphetamines, relapse rate, time-to-relapse or cumulative abstinence rate, as well as on reduction of ADHD symptoms.

Two double-blind placebo-controlled clinical trials with a total of 319 adolescents with a diagnosis of ADHD and a comorbid SUD (Table 1) have further assessed the efficacy of methylphenidate in dually diagnosed samples. In the first of these trials, a 6-week single-blind study with 16 adolescent males with ADHD and comorbid SUD, compared with placebo, ER-methylphenidate Spheroidal Oral Drug Absorption System was associated with a significant improvement in ADHD symptoms and in global functioning, although there was no significant effect on drug use.[59] More recently, a large 16-week, randomized, controlled, multisite trial evaluated the efficacy and safety of OROS-MPH compared with placebo associated to CBT in a sample of 303 adolescents (aged 13 to 18 y) meeting Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria for ADHD and SUD.[58] There were no group differences on reduction of ADHD symptoms or reduction in days of substance use, but OROS-MPH, that was well tolerated, was associated with modest improvements in some secondary outcome measures, such as parents ADHD ratings or urine toxicological screens.

Lisdexamfetamine dimesylate, a prodrug of D-amphetamine, is approved in different countries including the United States for the treatment of children, adolescents, and adults with ADHD. Lisdexamfetamine is a therapeutically inactive molecule, but after oral ingestion, by enzymatic hydrolysis, it is converted to L-lysine, a naturally occurring essential amino acid and a by-product of the hydrolysis, and active D-amphetamine, which is responsible for its therapeutic effects.[66] Because of its pharmacological characteristics that confers it a broader safety and tolerability profile and a reduced abuse potential relative to immediate-release psychostimulants,[67,68] it may be potentially useful in patients with dual diagnosis. To address this issue a recent study conducted a post hoc analysis on data from a large 4-week, placebo-controlled study[69] comparing the efficacy and safety of lisdexamfetamine dimesylate in adults with ADHD with or without a history of depression or SUD.[70] Of the 414 subjects included in the original study,[69] 17 participants, all by chance randomized to lisdexamfetamine reported a history of SUD. In these post hoc analyses the effectiveness of lisdexamfetamine in individuals with a history of SUD was similar to the overall study population.[70] Incidence of adverse events was also similar in subjects with and without a history of SUD and receiving lisdexamfetamine.

Atomoxetine in the Treatment of Patients With ADHD and Comorbid SUD

A few studies have assessed the efficacy and tolerability of atomoxetine in adolescent or adult patients with ADHD and a comorbid SUD (Table 2). In the first of these studies, a 12-week randomized controlled trial with a sample of patients with ADHD and comorbid alcohol abuse or dependence,[71] compared with placebo treatment with atomoxetine was associated with a significant improvement of ADHD symptoms. Moreover, the magnitude of the effect on symptoms of ADHD was similar to that observed in studies of atomoxetine treatment of ADHD in adults without dual disorders. Although there was a significant reduction in cumulative heavy drinking days of 26% compared with placebo over the 12-week study, there were no significant differences between the groups in time-to-relapse to heavy drinking. Similar results were reported in

TABLE 1. Methylphenidate in the Treatment of Patients With ADHD and Comorbid SUD

References	Study Design	Comparison	Adjunctive Therapy	Dose	Sample	Duration (wk)*	Key Findings
Levin et al[56]	Open-label	None	RPT	40-80 mg†	12 adults with ADHD+ cocaine dependence	12	8 subjects completed the study Improvement of ADHD symptoms and reduction of craving and cocaine use
Castaneda et al[55]	Open-label	FLX, BUP, SR-MPH, D-amphetamine, methampheta-mine	None	120 mg‡	19 adults with ADHD+ cocaine dependence	52	SR-MPH was most efficacious in reducing symptoms of ADHD, with minimal cocaine slips or side effects
Schubiner et al[64]	RCT (double-blind)	PLC	Weekly individual and group therapy	90 mg†‡	48 adults with ADHD+ cocaine dependence	12	Significant improvement of ADHD with MPH vs PLC. No significant group differences in self-reported cocaine use, urinalysis results, or cocaine craving
Somoza et al[57]	Open-label, multicenter	None	RPT	60 mg†	41 adults with ADHD+ cocaine dependence	10	70% completed the study. MPH was well tolerated, with improvement in ADHD symptoms and in cocaine dependence
Carpentier et al[60]	RCT, cross-over (double-blind)	PLC	None	45 mg†‡	25 adults with ADHD and various SUD	8	19 subjects completed the study. Similar clinical improvement with MPH (36%) and with PLC (20%). Significantly more side effects with MPH>PLC

TABLE 1. (*Continued*)

References	Study Design	Comparison	Adjunctive Therapy	Dose	Sample	Duration (wk)*	Key Findings
Levin et al[62]	RCT (double-blind)	SR-MPH vs. BUP vs. PLC	Individual CBT	80 mg‡	98 adults with ADHD in MMT	12	70% study completers. Reduction of ADHD symptoms in 3 groups; no significant differences between MPH, BUP, or PLC on ADHD or cocaine use outcomes
Levin et al[63]	RCT (double-blind)	SR-MPH vs. PLC	Individual CBT	60 mg‡	106 adults with ADHD+ cocaine dependence	14	The majority of patients reported an ADHD symptom improvement >30%, similar in both groups. ADHD symptom improvement with MPH (not with PLC) was associated with a reduction in cocaine use
Szobot et al[59]	RCT (single-blind, cross-over)	MPH-SODAS vs. PLC	None	1.2 mg/kg/d‡	16 adolescent males with ADHD and SUD	6	Significant improvement of ADHD symptoms and global functioning with MPH-SODAS vs. PLC. No significant effect on drug use
Konstenius et al[61]	RCT (double-blind)	OROS-MPH vs. PLC	RPT	72 mg‡	24 adults with ADHD and amphetamine dependence	13	Significant improvement in self-rated ADHD symptoms in both groups. No group differences in drug use (self-reported or by urine toxicology) or in craving. Good tolerability of OROS-MPH

Winhusen et al[65]	RCT (double-blind) multicentric	OROS-MPH vs. PLC	NTT+ brief smoking cessation therapy	72 mg‡	255 adults with ADHD and nicotine dependence	15	Significant reduction of ADHD symptoms with OROS-MPH vs. PLC. No differences in smoking abstinence rates between OROS-MPH (43.3%) and PLC (42.2%). Good tolerability of OROS-MPH
Riggs et al[58]	RCT (double-blind) multisite	OROS-MPH+ CBT vs. PLC+ CBT	CBT	72 mg‡	303 adolescents (13-18 y of age) with ADHD+ SUD	16	No significant differences between OROS-MPH and PLC on TDAH or drug use. Good tolerability of OROS-MPH

*Indicates study duration.
†Immediate-release methylphenidate (MPH).
‡Maximum daily methylphenidate dose.
ADHD indicates attention-deficit hyperactivity disorder; BUP, bupropion; CBT, cognitive behavioral therapy; FLX, fluoxetine; MMT, methadone maintenance treatment; MPH-SODAS, extended-release formulation of methylphenidate Spheroidal Oral Drug Absorption System; NTT, nicotine transdermal therapy; OROS-MPH, osmotic release oral system methylphenidate; PLC, placebo; RCT, randomized controlled trial; RPT, relapse prevention therapy; SR-MPH, slow-release methylphenyldate; SUD, substance use disorder.

ADDICTIVE DISORDERS & THEIR TREATMENT
Volume 12, Number 4
December 2013

TABLE 2. Atomoxetine in the Treatment of Patients With ADHD and Comorbid SUD

References	Study Design	Comparison	Adjunctive Therapy	Dose	Sample	Duration (wk)*	Key Findings
Wilens et al[71]	RCT (double-blind)	PLC	None	100†	147 adults with ADHD+ alcohol abuse or dependence	12	Significant improvement of ADHD symptoms and significant reduction of heavy alcohol use in the ATMX cohort compared with placebo. Good tolerability of ATMX
Levin et al[72]	Open-label	None	CBT	100†	20 adult patients with ADHD+ cocaine dependence	12	Significant reduction in ADHD symptoms. No effects on cocaine use. 2 subjects discontinued ATMX because of MAE
McRae-Clark et al[73]	RCT (double-blind)	PLC	MI	100†	38 adults with ADHD+ cannabis dependence	12	Significantly greater improvement of some ADHD symptoms with ATMX compared with PLC. No differences in marijuana use. The majority of MAE were mild to moderate in severity
Thurstone et al[74]	RCT (double-blind)	ATMX vs. PLC	MI/CBT	100†	70 adolescents (13-19 y of age) with ADHD+ comorbid SUD	16	No significant differences in ADHD scores or in substance use between ATMX and PLC. Rates of MAE were generally mild and short-lived
Adler et al[75]	Open-label	None	Residential rehab	120†	18 adult polysubstance users+ ADHD	10	12 residents completed ≥ 2 wk of treatment. ATMX was well tolerated and associated with improvement of ADHD symptoms and in some measures of craving

*Indicates study duration.
†Maximum daily atomoxetine dose.
ADHD indicates attention-deficit hyperactivity disorder; ATMX, atomoxetine; CBT, cognitive behavioral therapy; MAE, medication adverse events; MI, motivational interviewing; PLC, placebo; RCT, randomized controlled trial.

ADDICTIVE DISORDERS & THEIR TREATMENT

Volume 12, Number 4
December 2013

an open-label study with 20 actively using cocaine-dependent individuals meeting Diagnostic and Statistical Manual of Mental Disorders, fourth edition-TR criteria for ADHD where atomoxetine in conjunction with CBT was associated with a reduction of ADHD symptoms, but did not produce reductions in cocaine use.[72] In an additional 10-week open-label study conducted in 18 abstinent adults with cooccurring ADHD and SUD who were being treated at a residential treatment facility, atomoxetine (up to 120 mg/d) was associated with improvement of ADHD symptoms and in some measures of craving and was reasonably well tolerated.[75] Furthermore, similar findings were reported in a 12-week double-blind, placebo-controlled trial of a flexible dose of atomoxetine (up to 100 mg/d) in conjunction with motivational interviewing (MI) in 38 marijuana-dependent individuals with ADHD, who reported a significant improvement in some measures of ADHD, but no treatment group differences were noted in marijuana use outcomes.[72]

However, in another 12-week double-blind, randomized, placebo-controlled trial with 70 adolescents aged 13 to 19 years with ADHD and SUD who were also receiving MI/CBT for the SUD, there were no significant differences in ADHD or substance use change between the atomoxetine+ MI/CBT and placebo+ MI/CBT groups.[74] It is important to underpin that study completion rates and the safety and tolerability profile of atomoxetine for ADHD are reportedly comparable in patients with or without comorbid SUD.[71,75,76] In summary, evidence from several studies and across different drugs of abuse suggests that atomoxetine while efficacious for ADHD symptoms may have minimal effects on substance use outcomes. However, in most studies, patients received different forms of psychological interventions directed to the SUD and that may have had an impact on its own not solely on the drug use outcomes, but on ADHD, as well.[74]

Other Pharmacotherapies for Patients With ADHD and Comorbid SUD

α_{2A}-Adrenergic Receptor Agonists

In addition to psychostimulants and atomoxetine, other pharmacological agents have also been evaluated and are commonly used in the treatment of patients with ADHD with or without comorbid disorders. The first group of medications is an α_{2A}-adrenergic agonists, particularly guanfacine-ER, approved by the Food and Drug Administration for treating ADHD in children and adolescents of 6 to 17 years of age.[47] α_{2A}-adrenergic agonists, which are also approved for the treatment of hypertension in adolescents and adults, have been suggested as useful treatments for different psychiatric disorders, including Giles de la Tourette,[77] as an aid for smoking cessation,[78] or for the pharmacological management of opioid withdrawal syndrome.[79] Therefore, at least hypothetically, guanfacine may represent a reasonable therapeutic option for patients with ADHD and with comorbid abuse or dependence to certain substances.

Bupropion

Bupropion hydrochloride, particularly in its SR form is also potentially useful for patients with ADHD and dual diagnosis. This antidepressant, approved for use in patients with major depressive disorder and as an aid to smoking cessation,[80] has been reported to be effective and safe for the treatment of adults with ADHD, as evidenced in a systematic review with meta-analysis.[52]

Preliminary data from a 5-week open-label study with 13 adolescent boys with ADHD, conduct disorder, and comorbid SUD, in a residential treatment program suggested an improvement in ADHD symptoms associated with bupropion treatment, to a maximum daily dose of 300 mg.[81] Similar findings were reported in a 12-week single-blind trial with 11 adult patients with ADHD and comorbid cocaine dependence receiving bupropion (in daily dose ranging 250 to 400 mg) and individual relapse prevention therapy.[82] In this study bupropion was well tolerated, and associated with significant reductions in attention difficulties, hyperactivity, and impulsivity, as well as in self-reported cocaine use, cocaine craving, and in cocaine-positive urine toxicology results. The effectiveness of bupropion-SR (to a maximum daily dose of 400 mg) was further evaluated

in a 6-month open-label study in 14 adolescent outpatients with ADHD, SUD, and a comorbid mood disorder, showing clinically and statistically significant reductions in ADHD, depressive symptoms, and in substance use.[83] However, in a double-blind, 3-arm, 12-week trial, comparing the efficacy of SR-methylphenidate, bupropion-SR to placebo in a sample with 98 adult methadone-maintained patients with ADHD who were also receiving weekly individual CBT, there were no differences, in retention rates, or in reducing ADHD symptoms or additional cocaine.[62]

Modafinil

Modafinil is a psychostimulant, neurochemically and pharmacologically unrelated to methylphenidate and amphetamine-like stimulants indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work disorder.[84] Because of its wide and complex mode of action and favorable tolerability profile it has been assessed for different psychiatric disorders. Indeed, although not an approved indication, several randomized controlled clinical trials have evidenced the efficacy of modafinil for treating patients with ADHD.[53] In addition, data from experimental studies and from clinical samples have suggested the possible beneficial effects of modafinil for treating patients with cocaine or amphetamine addiction.[85,86] To date the limited evidence of the usefulness of modafinil for patients dually diagnosed with ADHD and a comorbid SUD comes from case reports.[87,88] In an initial report with a series of outpatient polysubstance abusers treated with modafinil included an amphetamine dependent patient and a cocaine dependent patient, both with comorbid ADHD.[87] In both cases there was a symptomatic improvement and a reduction of craving associated with modafinil treatment. More recently, a global and sustained clinical improvement has been reported after 1-year of follow-up in a single patient dually diagnosed with ADHD and amphetamine dependence treated with modafinil, at a total daily dose of 400 mg.[88]

Treatment of the SUD in Patients With ADHD

On the basis of the lack of efficacious and safe pharmacotherapies available for patients addicted to cocaine, metamphetamine or other amphetamine derivatives, and considering the well-established efficacy of opioid or nicotine agonists, for opioid and nicotine dependence, respectively, the possibility of using prescription stimulants as a treatment option for stimulant addiction has been considered.[89,90] Consequently, and based on the pharmacology of methylphenidate and atomoxetine, together with the results from experimental studies,[91] the efficacy of these medication as an aid for smoking cessation has been assessed in smokers with and without ADHD.

The efficacy of OROS-MPH (at a target dose of 54 mg/d) as a pharmacological aid for smoking cessation was assessed in an 8-week double-blind trial with 80 cigarette smokers without a diagnosis of ADHD. There were no differences compared with placebo in abstinence rates or in reducing withdrawal symptoms.[92] These results are consistent with the findings from a large randomized placebo-controlled multicenter trial that assessed the efficacy of OROS-MPH (at a 72 mg/d dose) as a coadjuvant treatment to the nicotine transdermal patch (21 mg/d) and brief individual therapy for smoking cessation in 255 adult smokers with a comorbid diagnosis of ADHD[65] (Table 1). Although the group taking OROS-MPH showed a significant reduction in ADHD symptoms and in the number of daily cigarettes compared with placebo, abstinence rates were similar in both the groups. However, when the results of this study were reanalyzed to explore racial/ethnic differences in OROS-methylphenidate, the rate of 4-week complete abstinence was significantly higher with OROS-MPH than placebo among nonwhites but not among white smokers with ADHD.[93] Furthermore, when examining smoking cessation response to OROS-MPH by ADHD subtype,[94] highly dependent smokers had significantly greater prolonged abstinence rates with OROS-MPH than with placebo in the ADHD combined-type

ADDICTIVE DISORDERS & THEIR TREATMENT
Volume 12, Number 4
December 2013

group but higher with placebo than with OROS-MPH in the predominantly inattentive group. However, abstinence rates did not differ by subtype or treatment among smokers who were less nicotine dependent. Therefore, methylphenidate could be a useful coadjuvant medication as an aid for smoking cessation in certain subgroups of patients with ADHD and nicotine dependence.

Bupropion-SR has also been assessed as an aid for smoking cessation in nicotine-dependent patients with a comorbid diagnosis of ADHD. Sixteen adolescents with nicotine dependence aged 12 to 19 years, 11 of with comorbid ADHD, were enrolled in a 6-week open-label study to examine the tolerability and feasibility of bupropion-SR (300 mg/d) along with 2 brief smoking cessation counseling sessions.[95] The study revealed the good tolerability and potential efficacy of bupropion-SR for adolescents with nicotine dependence and a diagnosis of ADHD. To date there are very few data on the efficacy of other pharmacotherapies approved for smoking cessation, such as varenicline, although this $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist has been suggested as a possible first-line treatment in dually diagnosed patients.[96] Also, there are no published reports on the efficacy of pharmacotherapies commonly used for treating withdrawal symptoms or in relapse prevention to other substances of abuse in dually diagnosed patients receiving treatment for ADHD.

Effect of Prescription Stimulants for Treating ADHD on the Risk of Developing an SUD

One of the more controversial issues of prescribing psychostimulants to children with ADHD is whether it may increase, decrease, or alternatively has no influence on the vulnerability to develop an SUD during adolescence or early adulthood. Some authors have suggested that treating ADHD with central nervous system stimulants during childhood may represent a risk factor for development of nicotine, alcohol, or other substance abuse later.[24,97] However, a vast majority of studies coincided in reporting that psychostimulant treatment in childhood is not associated with an increased risk of developing an SUD, or, as evidenced in a pivotal systematic review with meta-analysis, may even be associated with a significant reduction in the risk of developing an SUD during adolescence or early adulthood.[98]

In this meta-analysis, Wilens et al[98] included all 6 available prospective and retrospective studies, with at least 4 years of follow-up, of children, adolescents, and adults with ADHD, published until then, comprising a pooled sample of 674 medicated patients and 360 unmedicated patients, that had information related to childhood exposure to prescription stimulants and later SUD outcome in adolescence or adulthood. Treatment of ADHD was associated with a significant reduction in the risk to develop an SUD in adolescence and adult age, with a pooled odds ratio (OR) of 1.9 for patients with a diagnosis of ADHD treated with psychostimulants during childhood, therefore suggesting a protective effect towards the risk of developing an SUD in children with ADHD. A greater protective effect on the risk for a later SUD was seen in studies that followed subjects into adolescence (OR = 5.8), compared with those with follow-up into adulthood (OR = 1.4). Subsequent longitudinal studies have provided additional evidence of the reduction in the risk of developing an SUD during adolescence in psychostimulant-treated children with ADHD.[99,100] Other prospective longitudinal studies, with ≥ 10 years of follow-up of children treated with methylphenidate have provided further evidence of the putative beneficial long-term effects of pharmacological treatment,[101–103] revealing a significant positive association between age at treatment initiation and the risk with age at methylphenidate treatment and risk of developing an SUD.[103]

In summary, several lines of evidence suggest that prescription stimulants for ADHD do not increase the vulnerability to substance abuse or dependence, and rather may be associated with a reduction in the risk for the subsequent development of SUD, therefore providing a protective effect during adolescence—the period of heightened biological and epidemiological

vulnerability to addictive disorders.[104] However, treatment with psychostimulants may delay, but not suppress the risk for an SUD.[102] These protective effects of psychostimulants may be explained by their therapeutic actions on low self-esteem, academic problems, or conduct disorders—factors all independently associated with the vulnerability of an addictive disorder.[22,98,105,106] In addition, as suggested by a pilot controlled study, psychostimulant therapy may normalize the delay in cortical maturation characteristically reported in ADHD.[107] All these would provide the unique opportunity to initiate preventive programs specifically adapted to this complex and heterogeneous population of patients with ADHD.

Risks Associated With Pharmacotherapies for ADHD

As evidenced in open-label studies and randomized controlled trials, at the doses commonly used in clinical practice for treating adult patients with ADHD, psychostimulant medications[55–65] and atomoxetine[71–75] appear to be well tolerated and with a good safety margin for adequately managing outpatients with comorbid ADHD and SUD (Tables 1 and 2). However, the potential of abuse and the risk of severe adverse events, particularly in patients abusing psychoactive substances or receiving medications for other comorbid disorders raise some concern in clinical practice in the management of dually diagnosed ADHD patients.

Potential of Abuse and Risk of Misuse of Pharmacotherapies Used in the Treatment of ADHD

During the recent 2 decades, evidence has emerged of the abuse and diversion of prescription stimulants among different populations of adolescents and young adults.[108,109] Many studies, including a systematic review[108] have evidenced the increasing use of stimulant medications by secondary education and university students, with consumption rates in the previous year of 5% to 9% and of 5% to 35%, respectively. Although a proportion of these adolescents and young adults may abuse the stimulants for their reinforcing effects, the majority use them as ''cognitive enhancers,'' to improve their academic performance.[108–110] Nonetheless, although abuse prescription stimulants may occur in individuals with and without ADHD, the majority of students with a diagnosis of ADHD generally use their medication as prescribed.[111] Furthermore, despite the growing number of patients with ADHD receiving pharmacological treatment, abuse of psychostimulants in the clinical context is very limited.[112] Consequently, when appropriately used for treating ADHD, psychostimulants do not appear to lead to abuse.[113] In contrast, atomoxetine lacks any of the reinforcing effects and any abuse potential.[114]

In addition to its therapeutic actions in ADHD, through the potentiating noradrenaline and dopamine in the prefrontal cortex,[115] methylphenidate and amphetamine derivatives increase dopamine levels in the nucleus accumbens, similar to other drugs of abuse.[116] Indeed, laboratory studies have shown that methylphenidate and amphetamines are self-administered by laboratory animals,[117] and in humans there is evidence of the subjective and reinforcing effects of these psychostimulants.[118] The abuse potential of psychostimulants is mediated by a series of factors, including the dose,[116,119] pharmacokinetic characteristics, and route of administration of the different drugs,[68,119,120] certain sociodemographic characteristics and personality traits of the individual patient,[109,115,121] as well as the context, expectations, and motivation of drug intake.[122,123]

Risk of Severe Cardiovascular Events Associated With Medications for ADHD

Mild, but statistically significant increases in heart rate (4 to 10 bpm) and blood pressure (1 to 4 mm Hg) have been reported in patients, with a diagnosis of ADHD receiving prescription stimulants or atomoxetine.[124–129] These changes in cardiovascular parameters, seemingly of little clinical relevance, may occur primarily during the initial stages of medication and generally stabilize over the course of treatment.[128,130] Overall, the risks of severe cardiovascular events and sudden death in children, adolescents, or

ADDICTIVE DISORDERS & THEIR TREATMENT

Volume 12, Number 4
December 2013

adults, associated with medications used for ADHD are extremely low and benefits outweigh the risks.[125,128,131,132] In patients receiving methylphenidate, amphetamine derivatives, or atomoxetine for ADHD, there is no evidence of an increase in the QTc interval or of other types of arrhythmias,[128,130,132] including no cases of Torsades de Pointes.

Special care is only recommended when starting pharmacological medications in patients with a personal of family history of cardiovascular disease, or in those with comorbid disorders taking medications with a known risk of severe cardiovascular events, such as methadone. Furthermore, a blood test or an electrocardiogram is not routinely recommended, unless there is a clear clinical indication, as indicated by several clinical guidelines including the National Institute for Clinical excellence Guideline on Diagnosis and Management of ADHD in children, young people, and adults[33]; the joint position statement by the Canadian Paediatric Society; the Canadian Cardiovascular Society; and the Canadian Academy of Child and Adolescent Psychiatry[133,134]; or the European guidelines on managing adverse effects of medication for ADHD.[131]

Intervention Protocols and General Recommendations in Dually Diagnosed ADHD Patients

There are limited empirical evidences that clarify if patients with this dual pathology ought to initiate treatment for ADHD before, simultaneously, or after an abstinence period for the comorbid SUD. Although the few clinical guidelines available recommend a drug-free period before commencing pharmacological treatment for dually diagnosed ADHD patients,[135,136] empirical evidences supporting this recommendation are very limited. Indeed, more recent consensus guidelines[32] recommend on deciding treatment order based on the severity of ADHD and the comorbid disorder.

The different studies assessing the efficacy of pharmacotherapies for ADHD have shown that they are equally efficacious and well tolerated, generally in combination with psychological interventions, in patients with a comorbid SUD. Although the majority of studies coincide in showing the efficacy of these medications on symptoms of ADHD in dually diagnosed patients, the effects on substance use outcomes are more limited. However, pharmacological treatment of ADHD with stimulants or other medications may help individuals to remain and benefit from treatment for the addictive disorder. The good tolerability and safety profile of psychostimulants or atomoxetine in dually diagnosed patients and the scarcity of significant interactions of these medications suggest they can be easily associated with pharmacotherapies commonly used in the treatment of specific substance abuse or dependence.

The scope of treatment of patients with ADHD and another comorbid disorder should be based on a multidisciplinary and integrated approach, which could be summarized in the points as follows.

- Treatment has to be the result of the careful diagnostic assessment of ADHD and the comorbid disorders.
- When a severe or problematic SUD is present, it is necessary to treat and stabilize the patient first, which will allow reassessing the patient's diagnosis and treatment needs in relationship to the diagnosis of ADHD.
- Dually diagnosed patients need to be carefully assessed before prescribing psychostimulant medications for a diagnosis of ADHD and require to be monitored regularly, to detect any signs of medication misuse or diversion.
- Although psychostimulants in general are considered as first-line pharmacological treatments for adult individuals with a diagnosis of ADHD, long half-life preparations or slow-release formulations are preferable, particularly in high vulnerability dually diagnosed patients, as these maximize treatment adherence and minimize the risk of abuse by maintaining the plasmatic concentrations of the psychostimulants in thresholds of efficacy during longer periods of time and producing a tonic dopamine activation.[108,109,116,119]
- Despite the concerns that pharmacological treatment may constitute a

risk factor for substance abuse, solid basic and clinical evidence indicate that the treatment of ADHD with psychostimulants either has no effect or reduces the vulnerability of development an SUD in patients with ADHD.

- Atomoxetine, although considered as a second choice of treatment for adults with ADHD, should be considered as an alternative first treatment option in patients with comorbid SUD, especially in individuals who previously failed to methylphenidate or other stimulants and in those with a past history of prescription psychostimulants abuse.
- Other alternative pharmacological options in patients with ADHD and SUD may include modafinil or bupropion.
- Psychological interventions are essential when particularly directed to the comorbid SUD and are key elements within a multimodal approach of this dual disorder.

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ADDICTIVE DISORDERS & THEIR TREATMENT

Volume 12, Number 4
December 2013

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Volume 12, Number 4
December 2013

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