

ADHD PRACTICE GUIDE

Attention-deficit/hyperactivity disorder

Vol. 1 No. 3

July 2006

3-Issue CE Newsletter Series

Issue 3



Jointly sponsored by the University of Cincinnati College of Medicine
and Princeton Media Associates

Clinical Review: OSCAR G. BUKSTEIN, MD, MPH

Expert Interview: JOHN GRABOWSKI, PhD

Case Study: SAMUEL J. GOLDSTEIN, PhD

CLINICAL REVIEW

Treatment Considerations in Patients with Comorbid ADHD and SUD

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Attention-deficit/hyperactivity disorder (ADHD), a common neuropsychiatric disorder of childhood, adolescence, and adulthood, is frequently comorbid with substance use disorders (SUDs), particularly in adults.¹ With high rates of SUDs in the adult ADHD population,² it is necessary to address the pharmacologic treatment of ADHD within the context of comorbid SUD.

This review will discuss current clinical perspectives on the treatment of individuals with comorbid ADHD and SUDs through a discussion of the following key questions:

1. When should ADHD and SUD treatment begin in the comorbid individual?
2. Due to the lack of Food and Drug Administration (FDA)-approved medications for comorbid ADHD and SUD and the lack of randomized trials examining treatments specifically in this comorbid population, upon what clinical support should clinicians base treatment decisions?
3. With the mixed reports on whether treating ADHD will help manage the SUD or worsen it, what information can begin to assist clinicians in managing this comorbid population?
4. If clinicians do treat these individuals, what are the minimum requirements in a follow-up treatment plan?

Screening SUD Individuals for ADHD

Given the high prevalence of ADHD in patients in addiction treatment, all adolescents and adults in treatment for SUDs should be screened, and if needed, evaluated for a diagnosis of ADHD. Clinicians involved with SUD patients should develop skills in assessing for developmentally appropriate manifes-

tations and impairments associated with adolescent and adult forms of ADHD and should use appropriate instruments, including the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* and symptom rating scales, for ADHD diagnosis.³ The diagnosis of ADHD in individuals with SUDs is made within a comprehensive psychiatric evaluation, which should include inquiry into other psychiatric diagnoses commonly comorbid with SUDs, including mood disorders, anxiety disorders, and psychotic disorders.³

Caution should be taken in drug-seeking individuals with SUDs who may feign ADHD symptoms or an ADHD history and insist on stimulant treatment. When the SUD and ADHD are comorbid, the acute status of the patient may obscure the ADHD diagnosis, or the patient may have difficulty distinguishing his or her drug-induced cognitive status from his or her baseline cognitive status.

Treating ADHD Early Is Essential

Studies and clinical experience have confirmed that ADHD treatment in a patient with ADHD and an SUD can begin soon after the SUD has been stabilized.⁴ There may be cases in which it is necessary to begin ADHD treatment simultaneously, but medication should never be provided in isolation from psychosocial treatment directed at the patient's SUD. Data suggest initiating treatment for ADHD as early as feasible, as symptoms of untreated ADHD may affect the outcome of the SUD treatment. Untreated ADHD appears to be associated with more severe and longer duration of SUD, lower SUD remission rates, and more difficulty in SUD treatment. Preliminary data suggest that ADHD treatment may play a positive role in treating SUDs.^{5,6}

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CME Accreditation

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Statement of Need

In the treatment of adult attention-deficit/hyperactivity disorder (ADHD), the clinician must consider a variety of treatment options. The issue of stimulant versus nonstimulant use, as well as the options of short-acting or long-acting formulations, must be carefully considered before prescribing a medication for a patient diagnosed with ADHD. When ADHD is found to be comorbid with substance use disorder (SUD), this challenge becomes more complicated, as treatment choice and time of treatment initiation may impact both the ADHD and SUD symptoms. It is necessary to educate clinicians on the clinical considerations regarding treatment options, as well as the treatment challenges presented when ADHD and SUD are comorbid, in order to ensure the most appropriate medication will be prescribed for each patient.

Learning Objectives

After completing this activity, participants should be able to:

- Discuss the role of treating ADHD in SUD-ADHD patients
- Evaluate therapy initiation timing and treatment options for patients with comorbid SUD-ADHD
- Outline the factors that impact treatment choice
- List the necessary follow-up involved in treating SUD-ADHD patients

Release Date: July 31, 2006

Expiration Date: July 31, 2007

There is no fee associated with this activity.

Target Audience

This activity is designed for primary care physicians and psychiatrists.

Disclosure Information

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The faculty reported the following:

Dr. Bukstein: Grant support—Eli Lilly and Company, Ortho-McNeil Inc, Shire Pharmaceuticals; Consultant—Cephalon, Ortho-McNeil Inc, Shire Pharmaceuticals; Speakers bureau—Cephalon, Novartis, Ortho-McNeil Inc, Shire Pharmaceuticals

Dr. Grabowski: Honoraria—Alkermes, GlaxoSmithKline, Shire Pharmaceuticals

Dr. Murphy: Speakers bureau—Ortho-McNeil Inc

Dr. Goldstein has disclosed that he has no relevant financial relationships with any commercial interest.

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The University of Cincinnati College of Medicine and Princeton Media Associates require faculty to inform participants whenever off-label/unapproved uses of drugs or devices are discussed in their presentation. Dr. Bukstein has disclosed that he will discuss the off-label/unapproved uses of modafinil, bupropion, and tricyclic antidepressants for the treatment of ADHD. Dr. Grabowski has disclosed that he will discuss the off-label/unapproved use of d-amphetamine in the treatment of cocaine dependence. Drs. Goldstein and Murphy do not discuss off-label/unapproved use of any commercial products.

Grant Support

This activity is supported by an unrestricted educational grant from Shire Pharmaceuticals.

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CLINICAL REVIEW**Treatment Considerations****Examining Stimulants and Nonstimulants in the SUD-ADHD Patient**

A number of stimulants and 1 nonstimulant agent are FDA-approved for the treatment of ADHD and have shown efficacy for adults with ADHD,^{7,8} with stimulants remaining the most effective treatment options for ADHD in all ages.⁹ Some stimulant, nonstimulant, and eugeroic medications are currently used off-label in adults or adolescents or are being studied in ADHD and SUD patients. Open studies of both stimulant and nonstimulant agents show improvements in ADHD and SUD variables, although controlled, randomized trials have not been as promising.⁴ There is a paucity of literature using well-controlled studies, with only 3 controlled trials of stimulants in individuals with SUDs, 1 in adolescents and 2 in adults, and no published controlled studies of nonstimulants. The limitations of the available literature include high levels of participant dropout and possibly inadequate duration of treatment, as well as the possible existence of other psychiatric comorbidities, such as mood and anxiety disorders, with both ADHD or SUDs, which may limit effectiveness of medications.

Stimulants. Stimulants, such as methylphenidate and amphetamine, are listed as Schedule II agents by the Drug Enforcement Administration (DEA). A Schedule II agent is defined as: (A) *The drug or other substance has a high potential for abuse;* (B) *The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions;* and (C) *Abuse of the drug or other substances may lead to severe psychological or physical dependence.*¹⁰ Stimulant medications should be used with caution in patients with hypertension¹¹⁻¹⁴ and should not be used in patients with structural cardiac abnormalities, according to package inserts.^{15,16}

In a double-blind, placebo-controlled, randomized trial of the stimulant methylphenidate in cocaine-abusing ADHD patients, Schubiner et al reported significant reductions in ADHD symptoms ($P=.0039$) and a decline in cocaine craving when compared with placebo, although there was no difference in cocaine use.⁶

Other trials have found conflicting results on stimulants' effect on the SUD. In the randomized, double-blind, placebo-controlled trial of the stimulant pemoline (discontinued in the United States in October 2005 due to liver toxicity) in adolescents with comorbid ADHD and SUD, the stimulant medication was shown to improve ADHD symptoms but have little, if any, effect on substance use.¹⁷ Although pemoline has been

since taken off the market, these results, similar to those by Schubiner et al,⁶ demonstrate the need for specific SUD treatment in addition to ADHD pharmacotherapy.

In a 12-week, double-blind, randomized, placebo-controlled trial, 98 methadone-maintained adults with ADHD and cocaine dependence/abuse (53% of the sample) received either sustained-release methylphenidate, a sustained-release formulation of the nonstimulant antidepressant bupropion, or placebo.¹⁸ All received weekly individual cognitive behavioral treatment; 70% completed the trial.¹⁸ All 3 groups showed reductions in ADHD symptoms with no differences in outcome between the 3 groups.¹⁸

Abuse Potential of Stimulants. As evidenced by open-label and randomized trials of the use of stimulants for the treatment of ADHD in adults with SUDs, stimulant treatment did not result in worsening of the SUD.⁶ In the Levin et al study, there were no reports of misuse or worsening of cocaine use noted among those randomized to methylphenidate.¹⁸

The route of administration and the rates of onset and offset in the brain play critical roles in determining the risk of chemical dependency.¹⁹ Research on the influence of the onset rate of effects with stimulant use supports that the abuse potential of

sustained-release formulations may be less than with immediate-release formulations.²⁰ These findings suggest that the newer, longer-acting stimulants, such as extended-release methylphenidate, dexamethylphenidate extended release, or the extended-release formulation of mixed amphetamine salts, may have a lower abuse potential than immediate-release preparations of psychostimulants.

Eugeroic Drug. Modafinil, a prescription medication of the eugeroic drug class, is FDA-approved for the treatment of daytime sleepiness in narcolepsy and is listed as a Schedule IV agent by the DEA. A Schedule IV agent is defined as: (A) *The drug or substance has a low potential for abuse relative to the drugs or other substances in Schedule III;* (B) *The drug or substance has a currently accepted medical use in treatment in the United States;* and (C) *Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.*¹⁰ Labeling includes a precaution to avoid use in patients with a history of left ventricular hypertrophy or in patients with mitral valve prolapse who have experienced mitral valve prolapse syndrome when previously receiving stimulants.²¹ Trials with modafinil in children and adolescents with ADHD

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CLINICAL REVIEW**Treatment Considerations**

show improvement in ADHD symptoms with modafinil over placebo while demonstrating its safety and tolerability.²² Modafinil has been shown to have stimulant effects on specific areas of the brain, as well as an alerting effect that may ameliorate some of the vegetative symptoms of cocaine withdrawal.²³ Dose-related effects on inhibition in normal volunteers suggest a positive effect of modafinil in reducing impulsive responding, an effect noted in a similar study in patients with ADHD.²⁴ A double-blind, placebo-controlled trial in 62 cocaine-dependent men and women reported increased cocaine abstinence in the modafinil group.²⁵ Initial evidence suggests that modafinil has limited potential for large-scale abuse.²⁶

Nonstimulants. Several nonstimulants offer additional options, although the efficacy of these agents has yet to be tested in controlled trials in adults. Atomoxetine, a noradrenergic reuptake inhibitor with no evidence of abuse potential,²⁷ is the only nonstimulant FDA-approved for the treatment of ADHD in children and adults. The labeling for atomoxetine carries a warning for suicidal ideation in children and adolescents.²⁸ Clinical trials using atomoxetine in adolescents and adults with ADHD and SUDs are expected in the near future.

Bupropion is a noradrenergic and dopamine reuptake blocker with stimulant-like effects that is FDA-approved as an antidepressant, but has evidence of positive effects for ADHD.²⁹ As with other antidepressants, this prescription drug's labeling carries a warning for suicidality in children and adolescents.³⁰ Bupropion exhibits low abuse potential on physiological measures compared with dextroamphetamine.³¹ Data supporting bupropion's efficacy for smoking cessation, along with the FDA approval for the use of bupropion for smoking cessation, suggest the potential value of this agent for addictive disorders, including patients with SUD comorbid with ADHD, depression, and/or smoking behavior.³² Patients (N=11) in a 12-week, single-blind trial of bupropion reported a considerable decrease in cocaine use and craving.³³

Venlafaxine, a serotonin-norepinephrine reuptake inhibitor FDA-approved for the treatment of depression, generalized anxiety disorder, and social anxiety disorder, has been shown in a small, open trial to have mild effects in the treatment of ADHD in adults.³⁴ However, it was not well-tolerated by up to 39% of trial patients (7 of 18).³⁵ The labeling for venlafaxine also warns of suicidality in children and adolescents.³⁴

Treating the Comorbid Patient

The mixed literature on the effectiveness of treating ADHD in

the SUD patient does not support specific drugs, time for initiation, and length of therapy, but open-label and randomized trials and clinical experience are providing some guidance. An emerging criterion for selection of treatment is whether the patient has active, comorbid SUD; a history of SUD without active SUD; or neither active nor a history of SUD but who have used drugs recreationally in the past. A "history of SUD" is generally defined as a reasonable interval of remission of use

or symptoms (6-12 months). In adults with ADHD and active SUD symptoms and behaviors, especially those with a stimulant or cocaine dependence, nonstimulants are preferable to stimulants, given the absence of more substan-

tial evidence of stimulant efficacy in this population. For those with active SUD with poor response to nonstimulants, especially if uncontrolled ADHD symptoms appear to contribute to relapse or instability of the SUD, the use of extended-release or longer-acting stimulants with lower abuse liability and diversion potential is a reasonable option but must be utilized under careful scrutiny and ongoing monitoring.³⁶

Individuals whose SUD is stable or who have a history of SUD may benefit from first-line stimulant treatment. Use of longer-acting or extended-release formulations of stimulants in this population would also be preferable.

The antidepressants such as bupropion and venlafaxine should be reserved as tertiary agents, for those not responding adequately to the first-line medications.

Avoiding Diversion and Abuse

The prevalence of stimulant abuse or dependence among adolescents or young adults with a history of ADHD and therapeutic stimulant use is very low.³⁷ In the absence of clear evidence of ongoing diversion (misuse and reselling) or high-risk situations (eg, family member with an active SUD, antisocial personality disorder in the patient or family members), the threat of or potential for diversion should not be the sole reason for withholding or not using stimulant medications. Rather, the clinician should always evaluate for these risk factors for diversion and set up a clear plan of control and administration of the stimulant (or other) medication. Clinicians should monitor prescriptions carefully with high suspicion directed toward early requests for refills or lost prescriptions. The treating physician must require frequent follow-up for all adult ADHD-SUD patients; questionnaires, objective toxicology screens, and contingency plans are suggested. These patients may benefit from relapse prevention techniques that take their impulsivity into account. Other cognitive-behavioral approaches may also be useful.

“Medication should never be provided in isolation from psychosocial treatment directed at the patient’s SUD.”

Conclusion

Identifying and treating comorbid ADHD and SUD is an important consideration. Comorbidity of ADHD and SUD can be treated with many of the modalities and medications used for adults with ADHD alone. But clearly, there are limitations to the literature regarding use in comorbid ADHD-SUD populations and the choice of agent and formulation. Further research

is necessary; however, the relative absence of abuse or worsening of the SUD when the patient is being treated for the ADHD is reassuring. In order to ensure proper treatment of both conditions, clinicians need to consider the timing of ADHD treatment as well as the possibility of diversion or abuse. Medication should never be provided in isolation from psychosocial treatment directed at the patient's SUD. ■

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EXPERT INTERVIEW with John Grabowski, PhD**The Potential for Concurrent Treatment with Comorbid ADHD and SUD**

John Grabowski, PhD, Professor of Psychiatry, Substance Abuse Research Center, Department of Psychiatry, University of Texas Medical School at Houston, University of Texas Health Science Center, is a clinical researcher in the field of substance abuse and is currently studying the effects of stimulant treatment in patients with comorbid attention-deficit/hyperactivity disorder (ADHD) and substance use disorder (SUD).

Q *Based on your involvement in substance abuse research and your clinical experience, how does the presence of a current SUD affect the treatment of ADHD with stimulant medications?*

A Individuals with a history of illicit opioid use maintained on methadone are behaviorally and biologically stabilized by this treatment. However, they develop tolerance to some opioid effects and may even become hyperalgesic. If comorbid conditions occur requiring treatment of pain, these patients will likely require more opioid rather than less, a fact often overlooked in clinical settings. In the case of patients diagnosed with stimulant abuse or dependence SUDs, maintenance therapy with stimulant medication may also be beneficial. Our data suggest that a stable stimulant therapy regimen, for example with sustained-release d-amphetamine, can reduce stimulant abuse in this population. Presumably this also reflects behavioral and biological stabilization. They too, become less, not more likely, to engage in illicit stimulant abuse. Treating ADHD likewise stabilizes neurochemical systems and behavior. When there is a convergence of 2 different diagnoses, in this example stimulant SUD and ADHD, the potential to treat both problems with the same medication is a bit of a coup. Problems, such as drug interactions and medication compliance, can be reduced. An additional critical question concerns optimal dose: will it be higher or the same as that necessary for either disorder alone? To date, our optimal sustained-release d-amphetamine dose for stimulant dependence has been 60 mg, which is within the recommended dosing range for ADHD.

Q *How did your research of substance abuse lead to your research team examining ADHD and the effects of stimulant treatment on comorbid ADHD and SUD?*

A We became involved through our examination of stimulant SUDs in preclinical research, human laboratory research, and clinical trials. In all of our initial clinical trials of sustained-release d-amphetamine for cocaine dependence, we

explicitly excluded individuals with an ADHD diagnosis. Inclusion would have been a confound; we would not have known whether we had succeeded in treating ADHD with a secondary effect on SUD. At this point, we have conducted several successful double-blind, placebo-controlled studies administering sustained-release d-amphetamine at various doses for various lengths of time for cocaine dependence treatment. Colleagues in Australia and the United Kingdom have also reported some success in the treatment of d-amphetamine dependence. Discussions with our colleagues, Frances R. Levin, MD, at Columbia University and Timothy E. Wilens, MD, at Harvard University, suggested that clear questions and problems in the ADHD field warranted further investigation of potential d-amphetamine efficacy in the dual-diagnosis patients.

Given the data that there is benefit to administering dextroamphetamine to someone with an SUD to diminish drug abuse, and an abundance of data that stimulants are effective in treating ADHD, it seems appropriate to examine amphetamine therapy as first-line treatment for the combined disorders, both of which seem to be responsive to a stable regimen of amphetamines.

“In the case of patients diagnosed with stimulant abuse or dependence SUDs, maintenance therapy with stimulant medication may also be beneficial.”

We are now developing a large, 2-site, double-blind, placebo-controlled trial at the University of Texas Health Science Center-Houston and Columbia University, with Dr. Levin as the other lead investigator, and Dr. Wilens as a consultant. We will enroll adult subjects with a history of ADHD, who also have a diagnosis of cocaine abuse or dependence. The study will examine the effects of treating both ADHD and SUD with sustained-release d-amphetamine.

A critical clinical issue in the ADHD field has been concern and unwillingness to administer stimulants to ADHD patients with current, or even a history of stimulant abuse. Our research may demonstrate that not treating these comorbid conditions with stimulants, but rather requiring patients to be abstinent from substance use for 6 months or more before giving them a stimulant, may in fact not be the most beneficial standard of treatment. ■

CASE STUDY**Treating Adult ADHD**

Samuel J. Goldstein, PhD, Clinical Assistant Professor of Psychiatry, Department of Psychiatry, University of Utah, Neurology, Learning, and Behavior Center

Case Overview A high percentage of adults self-referred for ADHD often have a history of diagnosis and treatment in childhood. Many of these adults have not received nor sought treatment since childhood, yet continue to struggle with symptoms at a mild to moderate level of impairment. The case description below is typical of this population.

Case Description J.O., a married, 34-year-old college graduate, business executive, and father of 3 children sought evaluation for ADHD. He reported to the clinician a childhood diagnosis of ADHD and subsequent treatment through high school. After high school, he sought no further medical or psychological treatment for his condition. He took an extra year to graduate college and entered the work force as a commercial realtor. He proceeded to work for the same company for the next 8 years, and works there still. Although he did his work well, J.O. had been repeatedly passed over for promotion because he was told he did not possess the attention to detail necessary to supervise others. J.O.'s wife also reported a history throughout their marriage of his difficulty sustaining attention, forgetting details, missing deadlines, and significant disorganization at home. A careful history, combined with the results of a psychological and personality assessment, determined that J.O. continued to meet symptoms and impairment for the Inattentive Type of ADHD.


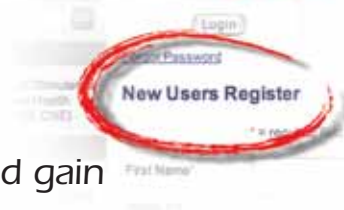
Case Discussion Similar to J.O., a significant number of individuals with ADHD continue to experience symptoms related to inattention and consequent impairment. Many of these individuals develop effective coping and related strategies reducing their perceived level of impairment, yet nonetheless leaving them with continued daily struggles. Though J.O.'s level of impairments might be considered mild relative to others receiving this diagnosis, they were associated with global difficulty beyond simple inattention.

While a medication may be viewed as the best first-line agent

based on research data for adults with generally uncomplicated ADHD such as J.O.'s, clinicians must recognize that each patient has the potential for different perceptions of the medication's efficacy and severity of adverse effects. When a particular medication causes adverse effects or is ineffective in a particular patient, there are a number of approved and off-label preparations available to consider. Additionally, the combination of medication and cognitive behavioral therapy is a research supported first-line, mainstay set of treatments for ADHD. Self-education is also a critical component of this treatment plan.

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2006-146-3



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