

ADHD PRACTICE GUIDE

Attention-deficit/hyperactivity disorder

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Issues 4 and 5 of the *ADHD Practice Guide—ADULT ADHD EDITION* address challenges in the diagnosis and treatment of comorbid major depressive disorder and attention-deficit/hyperactivity disorder (ADHD). This continuation of the original 3-issue newsletter series provides clinicians with further education on the importance of addressing adult ADHD, with a specific focus on the impact of comorbid psychiatric conditions in this undertreated patient population.

CLINICAL REVIEW

Improved Outcomes in the Diagnosis and Treatment of Depression and Comorbid ADHD

Based on a presentation by Andrew A. Nierenberg, MD, Medical Director, Bipolar Clinic and Research Program, Massachusetts General Hospital, Associate Professor, Harvard Medical School

Major depressive disorder (MDD) is one of the most common psychiatric diagnoses in the United States. Attention-deficit/hyperactivity disorder (ADHD)—one of the most prevalent childhood health disorders—frequently persists, undiagnosed, into adulthood, and many individuals remain untreated. A growing awareness of the extent to which MDD and adult ADHD coexist has highlighted the need for clinicians to consider both diagnoses when assessing patients in whom either condition is suspected. Given the significant and sometimes dangerous symptoms in patients with these conditions, systematic assessment and careful selection of therapy are warranted. An understanding of both distinct and overlapping symptoms of these conditions will help clinicians make a differential diagnosis, which will then determine appropriate treatment options for the patient. Considering the current high rate of underdiagnosis and undertreatment of ADHD in adults, comprehensive assessment and optimal management strategies are crucial.

Clinical and Economic Burden of MDD and ADHD

Research indicates that MDD affects approximately 5% to 7% of US adults, and that women are twice as likely as men to experience MDD.^{1,2} According to the National Institute of Mental Health, MDD is the leading cause of disability in the United States for individuals 15 to 44 years of age. While MDD can develop at any time, the median age of onset is 32 years of age.³

Individuals with MDD are more likely to report poorer health and a lower quality of life than nondepressed individuals. In addition, MDD is associated with insomnia, fatigue, weight fluctuation, and persistent physical symptoms that do not

respond to treatment, such as headaches, digestive disorders, and chronic pain.⁴

ADHD can cause a pattern of chronic impairment in multiple domains, significantly impacting the patient's quality of life. ADHD is also associated with a high prevalence of comorbidities, particularly related to other mental disorders, including MDD, and a risk of substance abuse.⁵ Data indicate that compared with adults without ADHD, adults with ADHD experience greater deficits in self-care, mobility, and cognition; a higher number of lost workdays; productive role impairment; and social role impairment.⁵ When comparing adults with ADHD with a control group, Able et al found that ADHD patients had higher rates of comorbid illness and greater functional impairment, including significantly higher rates of problem drinking, lower educational attainment, and greater emotional and interpersonal difficulties.⁶

Recent studies have also suggested that adults with ADHD may experience a higher incidence of legal problems than adults without ADHD. In a comparison study of 4 groups of adults (no ADHD, subthreshold ADHD, late-onset ADHD, and full ADHD), Faraone et al found that almost 50% of adults with full ADHD and about 35% of adults with late-onset ADHD had either been arrested, convicted, or imprisoned, compared with less than 10% of adults without ADHD.⁷

Furthermore, persistent symptoms of inattention associated with ADHD have been found to result in significant conse-

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CME Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the University of Cincinnati and Princeton Media Associates. The University of Cincinnati is accredited by the ACCME to provide continuing medical education for physicians.

The University of Cincinnati designates this activity for a maximum of 1 *AMA PRA Category 1 Credit*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Target Audience

This activity is designed for psychiatrists.

Statement of Need

Major depressive disorder (MDD), which affects approximately 5% of the American adult population, is one of the most commonly encountered psychiatric conditions in the United States. Attention-deficit/hyperactivity disorder (ADHD), a common childhood health disorder, has been shown to persist, particularly in symptoms of inattention, into adulthood. ADHD is also often associated with psychiatric comorbidities, including MDD.

Despite a documented high incidence of comorbid ADHD, individuals with MDD are underdiagnosed with the comorbid condition due in part to the lack of systematic screening for ADHD in this population. This underdiagnosis, in combination with the need for increased awareness of adult ADHD and its related treatment options, not only impacts ADHD outcomes, but also may limit the effectiveness of MDD management.

Due to the challenges presented by these comorbid conditions, psychiatrists require education on the burden of MDD and ADHD in the United States, the frequency at which these conditions occur comorbidly, and effective pharmacologic and psychosocial treatment strategies.

Learning Objectives

After completing this activity, participants should be able to:

- Describe the burden of MDD and comorbid ADHD
- Articulate the common challenges associated with screening, diagnosing, and treating MDD and comorbid ADHD
- Implement effective tools and methods to aid in the effective diagnosis of comorbid ADHD in individuals with MDD

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There is no fee associated with this activity.

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The University of Cincinnati and Princeton Media Associates require faculty to inform participants whenever off-label/unapproved uses of drugs or devices are discussed in their presentation.

The following off-label/unapproved drugs or devices are discussed: methylphenidate (all formulations), dexamethylphenidate immediate release, mixed amphetamine salts immediate release, and dexamphetamine in the treatment of adult ADHD.

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CLINICAL REVIEW

Depression and Comorbid ADHD

quences when operating a motor vehicle. A study of 25 young adults with ADHD found that compared with a control group, ADHD subjects were much more likely to incur traffic violations and speeding violations, drive while intoxicated, have their driver's licenses suspended, and/or cause an accident.⁸ It appears that adults with ADHD may be prone to engage in higher-risk behaviors, with a potential negative impact on their health or the welfare of the community at large.

The economic burden related to the direct and indirect costs of MDD is substantial. A 2006 literature review of cost-of-illness studies of MDD indicated that the average annual cost per case ranged from \$1000 to \$2500 in direct care costs, from \$2000 to \$3700 in morbidity costs, and approximately \$200 to \$400 in mortality costs.⁹ Greenberg et al estimated the cost of depression to be \$83.1 billion in 2000, of which \$26.1 billion were direct costs.¹⁰ In addition to healthcare costs, lost productivity due to MDD is considerable. The workplace cost of depression was estimated at \$51.5 billion in 2000.¹⁰ National Comorbidity Survey Replication Study data revealed that individuals with MDD averaged 27.25 lost workdays annually, and additional projections estimated that MDD accounts for 225 million lost workdays and \$36.6 billion in lost salary-equivalent productivity each year.¹¹ Another study compared the job performance and productivity of employed patients with depression and dysthymia against that of healthy controls over 18 months; while job performance improved as depression symptoms declined, even improved depressed patients performed poorly compared with healthy controls on mental, interpersonal, time management, output, and physical tasks.¹²

As with MDD, ADHD is also associated with an increased economic burden. Annual estimated excess per capita healthcare, disability, and lost productivity costs of treated ADHD patients 7 to 44 years of age and their family members was \$31.6 billion, according to a 2005 study.¹³ A literature review performed by Matza et al found that adults with ADHD had substantially higher annual medical costs (\$4929-\$5651) than matched controls (\$1473-\$2771) and found that other costs associated with ADHD included those related to legal issues, psychiatric and medical comorbidities, motor vehicle accidents, and lost work productivity.¹⁴

The consequences of ADHD and MDD when presenting comorbidly also have a substantial clinical and economic impact. Fischer et al interviewed 322 adults with ADHD and found that subjects with both ADHD and MDD had a higher

frequency of anxiety disorder and social phobia and were more likely to have received both psychotherapy and pharmacologic treatment prior to enrollment in the study when compared with ADHD patients without MDD.¹⁵

ADHD in Adults

ADHD is one of the most common mental disorders in children and adolescents. The National Institute of Mental Health reports that ADHD usually becomes evident in preschool or early elementary years. While the median age of onset of ADHD is 7 years of age, the disorder can persist into adolescence and adulthood³—up to 70% of children with ADHD will continue to be symptomatic as adults.¹⁴ The prevalence of adult ADHD is estimated to be 4.4%, with only 10% of individuals currently diagnosed receiving treatment. Adult ADHD occurs more frequently in men than in women, with an odds ratio of 1.6.⁹



The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* divides the criteria for ADHD diagnosis into 2 categories: inattention and hyperactivity/impulsivity.¹⁶ Although symptoms in both categories are usually present in child-

hood, some typical symptoms may affect adults more frequently than others. Several studies have proven that of the various ADHD symptoms, those associated with inattention are most likely to persist into adulthood. Biederman et al studied symptom decline in ADHD patients with different definitions of remission and found that symptoms of inattention remitted for fewer subjects than did symptoms of hyperactivity or impulsivity.¹⁷ Millstein et al assessed 149 adult ADHD patients and found that inattentive symptoms existed in over 90% of subjects, while only about 50% exhibited hyperactivity symptoms.¹⁸

Comorbid MDD, ADHD, and Mood Disorders

The prevalence of MDD and other mood disorders in the adult ADHD population in comparison to non-ADHD controls is a growing area of research. Studies of these patient populations clearly indicate that mood disorders occur more frequently in patients with ADHD than in the non-ADHD population.^{9,11,19,20} The same trend emerges when looking at the rate of ADHD in patients with diagnosed mood disorders versus those without mood disorders.^{9,21}

The National Comorbidity Survey Replication Study found that 38.3% of individuals with a primary diagnosis of ADHD during the previous 12 months also had a mood disorder, compared with 5% of subjects without ADHD.⁹ In particular, 18.6% of

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TABLE 1
Prevalence of Mood Disorders with ADHD⁹

Comorbid Condition	Patients with ADHD Who Have Comorbid Condition (%)	Patients without ADHD Who Have Comorbid Condition (%)
MDD	18.6	7.8
Dysthymia	12.8	1.9
Bipolar Disorder	19.4	3.1
Any Mood Disorder	38.3	5.0

ADHD = attention-deficit/hyperactivity disorder; MDD = major depressive disorder.

individuals with a primary diagnosis of ADHD during the previous 12 months also had MDD, compared with only 7.8% of the non-ADHD subjects. Rates of other mood disorders in patients with and without ADHD are outlined in **Table 1.**⁹

Biederman further demonstrated that the presence of ADHD in girls increases the risk of psychotic, mood, and anxiety disorders in young adulthood.¹⁹ Estimates of the cumulative lifetime prevalence adjusted for age and socioeconomic status increase over time indicate that by age 20, approximately 60% of subjects had one of these disorders compared with approximately 25% of the control group.¹⁹ A study that assessed lifetime ADHD and comorbid psychopathology in 435 parents of children with ADHD found that 59% of parents with ADHD had MDD, compared with 40% of parents without ADHD ($P=.0003$).²⁰

Furthermore, onset and degree of ADHD may impact the incidence of comorbid MDD. Faraone et al found that 35% of patients with late-onset ADHD (presentation after age 7 but before age 12) and 33% of patients meeting full criteria for ADHD also had MDD, but only 10% of subthreshold patients were affected.¹¹

The prevalence of ADHD in patients with mood disorders is also high. In a study led by researchers at Massachusetts General Hospital, 16% of adult subjects with a primary diagnosis of MDD were found to have a lifetime history of ADHD.²¹ MDD patients with ADHD comorbidity more frequently had a history of dysthymia, were more likely to abuse alcohol or drugs, and had a greater number of personality disorders than those with MDD alone.²¹

Additional data from the National Comorbidity Survey Replication Study found that 9.4% of patients diagnosed with MDD during the previous 12 months also had a diagnosis of ADHD, compared with 3.7% of those without MDD who had a

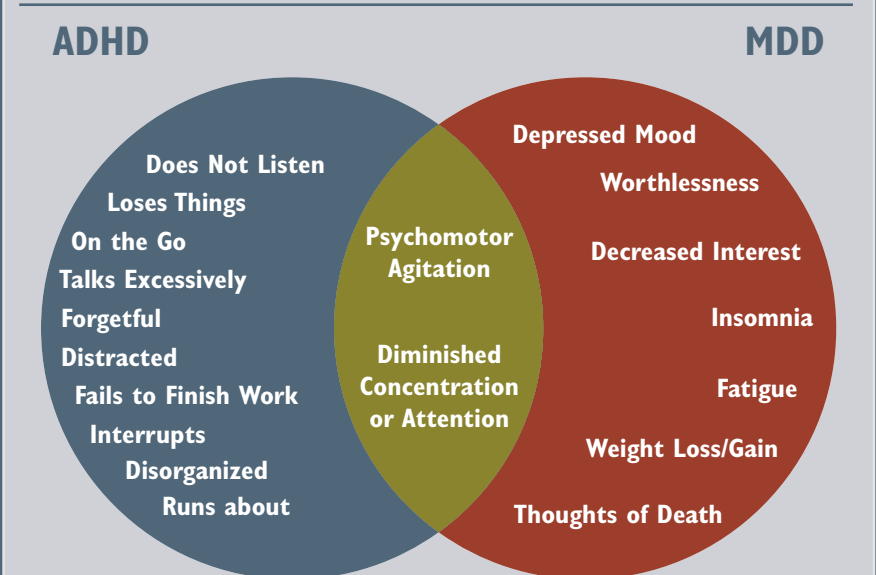
diagnosis of ADHD.⁹ Rates of ADHD in patients with and without other mood disorders are outlined in **Table 2.**⁹

Overlapping Symptoms and Differential Diagnosis

Comorbid ADHD and mood disorder diagnoses often persist even after correcting for overlapping symptoms, such as distractibility, inattentiveness, physical restlessness, and talkativeness. Since *DSM-IV* ADHD criteria do not include a mood component, these symptoms must be carefully examined as a possible comorbid mood disorder.

Proper diagnosis of comorbid MDD and adult ADHD relies upon recognizing which symptoms are attributable to each disorder. Although 2 symptoms of both ADHD and MDD—psychomotor disturbance and diminished ability to concentrate—

FIGURE
Overlap of DSM-IV Criteria¹⁶



DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ADHD = attention-deficit/hyperactivity disorder; MDD = major depressive disorder.

overlap, many ADHD symptoms are not involved in MDD, and conversely many MDD symptoms are not characteristic of ADHD patients. Therefore, clinicians must perform a systematic assessment of ADHD so as not to misdiagnose these symptoms and to ensure a comprehensive differential diagnosis, particularly in adults (Figure).¹⁶

Differential diagnosis is crucial for selecting appropriate treatment in patients with potential comorbid MDD and ADHD. The following should be considered when performing a differential diagnosis of these conditions:

- *Hyperactivity*—Associated with both conditions, although more frequently in ADHD, hyperactivity in MDD is often characterized by restlessness, usually related to anxious rumination
- *Inattention*—Associated with both conditions
- *Talkativeness*—Associated with ADHD; talkativeness is only associated with MDD in cases of mania or hypomania
- *School dysfunction*—Associated with ADHD; may be present in MDD depending upon the individual
- *Effect of structure*—The symptoms of ADHD can decline with structure and escalate in an unstructured environment; the effect of structure is less certain in MDD
- *Oppositional defiant or conduct disorder*—Associated with both conditions, especially in children; in particular, MDD in children can be associated with irritability
- *Age of onset*—Typically under 7 years of age in ADHD, although possibly up to 12 years; variable in MDD
- *Course*—Constant with ADHD; chronic or cyclic with MDD
- *Irritability*—Associated with both conditions, although often more frequently in MDD
- *Substance abuse*—Associated with both conditions, with higher risk in young adults
- *Global dysfunction*—Associated with both conditions
- *Family history of ADHD*—Associated with both conditions
- *Family history of MDD*—Associated with both conditions

Milberger et al assessed the extent of symptom overlap between ADHD and the disorders that frequently coexist with ADHD, including MDD, by re-diagnosing subjects on the basis of 2 techniques that corrected for the overlapping symptoms; 79% of subjects maintained their ADHD diagnosis when the overlapping symptoms were eliminated.²²

ADHD, MDD, and other mood disorder comorbidities often lead to several functional impairments in adults. In particular, the symptom domains in ADHD—hyperactivity, inattention, and impulsivity, combined with the psychiatric comorbidities of anxiety, mood disorders, and disruptive behavior—lead to social, academic, professional, and personal difficulties, as well as self-destructive behaviors that may persist as individuals move into young adulthood and beyond. The presence of ADHD can be masked by mood disorders; if clinicians do not systematically screen for ADHD, treatment will be suboptimal and patient functionality will continue to be impaired.

Diagnostic Considerations

Diagnosing comorbid ADHD in adult patients with MDD is challenging due to the lack of systematic diagnosis of comorbid disorders in routine care; the underuse of systematic assessments for childhood-onset disorders; and the error of omission by clinicians in failing to consider ADHD as a possible diagnosis. Inattention may be attributed to the mood disorder, while dysfunction and interpersonal difficulties may be mistakenly attributed to a developmental or personality disorder.

The practical challenges of routine screening for ADHD of all patients with mood disorders are considerable. Clinicians who do not currently screen MDD patients for ADHD may find it difficult to change existing practice patterns. Nevertheless, finding ways to operationalize screening in practice is a worthwhile undertaking, and several tools are available to assist clinicians in screening for ADHD in adult patients with MDD or other mood disorders. Multiple trials have suggested the use of Adult ADHD Self-Report Scale (ASRS), a self-report screening scale of adult ADHD developed by the World Health Organization, which has provided accurate assessments in screened populations.^{23,24} The ASRS Version 1.1 Screener is a subset of the original 18-question symptom checklist.²⁵ This tool includes 6 simple questions, answered on a 5-point scale from “none/never” to “very often,” that clearly identify the most prevalent challenges faced by adults with ADHD (Table 3). Other examples of diagnostic interview tools and rating scales include the Attention Deficit Hyperactivity Disorder Rating Scale, Barkley Adult ADHD Rating Scale, Conners’ Adult ADHD Rating Scale, Wender-Reimherr Adult Attention-Deficit Disorder Scale, and Brown ADD Scale Diagnostic form.

TABLE 2
Prevalence of ADHD with Mood Disorders⁹

Primary Diagnosis	Patients with Comorbid Condition also Diagnosed with ADHD (%)	Patients without Comorbid Condition also Diagnosed with ADHD (%)
MDD	9.4	3.7
Dysthymia	22.6	3.7
Bipolar Disorder	21.2	3.5
Any Mood Disorder	13.1	2.9

ADHD = attention-deficit/hyperactivity disorder; MDD = major depressive disorder.

TABLE 3**ASRS Version 1.1 Screener²⁵**

- **How often do you have difficulty wrapping up the final details of a project once the challenging parts have been done?**
- **How often do you have difficulty getting things in order when you have to do a task that requires organization?**
- **How often do you have problems remembering appointments or obligations?**
- **When you have a task that requires a lot of thought, how often do you avoid or delay getting started?**
- **How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?**
- **How often do you feel overly active and compelled to do things, like you were driven by a motor?**

ASRS = Adult Attention-Deficit/Hyperactivity Disorder Self-Report Scale.

Several tools also exist for MDD screening, including the Patient Health Questionnaire 9, which screens for the 9 symptoms of MDD (Table 4). The Quick Inventory of Depressed Symptomatology Self-Report and the Beck Depression Inventory are also commonly used.²⁶⁻²⁸ Clinicians may use these tools to screen for MDD in patients with ADHD as well as to track MDD symptoms and outcomes.

Challenges of Treatment

Inattention and dysfunction symptoms are likely to persist in patients whose MDD is diagnosed but whose ADHD remains undiagnosed and, therefore, untreated. Similarly, patients who are treated for ADHD but whose depression is not addressed will experience a continuation of their depressive symptoms and associated consequences. Unfortunately, many patients in whom MDD and ADHD occur comorbidly are never treated appropriately for both conditions, both due to the lack of differential diagnosis of ADHD in MDD patients and the low rate of treated patients with adult ADHD. The challenges of treating these conditions when they occur comorbidly revolve around identifying and optimizing the appropriate treatment strategy for the individual patient.

The primary challenge in treatment is identifying the correct therapeutic options for the patient. Managing both ADHD and MDD involves focused combination therapy targeted directly at individual patient requirements; simple polypharmacy is often insufficient or ineffective and can delay symptom resolution. Treatment targets should be prioritized based on the severity of each comorbid disorder and the impact of each treatment option on both conditions.

A second challenge is optimizing the value of treatment, which requires careful measurement and tracking of the patient's progress. Only by monitoring symptoms can clinicians and patients determine if alterations in therapeutic options or dosing are required. This can be accomplished via use of ADHD and MDD rating scales to track a patient's symptom severity over the course of treatment.

A final concern is the use of stimulants to treat ADHD and comorbid depression. Stimulants are often prescribed as ADHD treatment; however, there is a risk of stimulant abuse in patients with MDD, particularly in patients with a history of substance or alcohol abuse or dependence. In these cases, diagnostic prioritization, based on which condition causes the most impairment for the individual patient, and alternative treatment options will play a larger role.

Treatment Options

Multiple drug classes are approved for the treatment of MDD and ADHD. Treatment options for MDD include selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, bupropion, tricyclic antidepressants, and cognitive behavioral therapy or interpersonal therapy for the treatment of depression.²⁹ Effective treatment options for ADHD include methylphenidate- and amphetamine-type stimulants and atomoxetine. The stimulant treatment options are available both in short- and long-acting formulations; however, the long-acting formulations have largely replaced their short-acting counterparts as first-line treatment for ADHD in clinical practice.

Methylphenidate. Methylphenidate is a short-acting drug, but various long-acting formulations have been developed to help ensure a constant level of the agent in the blood. Several studies have indicated the effectiveness of these formulations in treating adults with ADHD.

Spencer et al conducted a randomized, 6-week, placebo-controlled, parallel study of methylphenidate in 146 adult patients with ADHD to determine the impact of dosing on efficacy.³⁰ At a dose of 1.1 mg/kg per day, researchers found that therapeutic response in terms of reducing inattention and hyperactive/impulsive symptoms in the methylphenidate group greatly exceeded the placebo response (76% vs 19%).³⁰ Improvement in symptoms began at about 2 weeks, with continued improvement over the 6-week study period.³⁰

A randomized, placebo-controlled study of once-daily oral release osmotic system (OROS) methylphenidate conducted by Biederman et al found that 66% of subjects receiving OROS methylphenidate compared with 39% of subjects on placebo attained a response of much or very much improved on the Clinical Global Impression-Improvement scale. The same percentages from each group also attained a greater than 30% reduction in the Adult ADHD Investigator System Report Scale score.³¹ Drug response rates ranged from 65% to 75%, based on the scoring system used.³¹

Similarly, dexamethylphenidate has proven effective in randomized studies. An examination of 221 adult patients randomized to

dexmethylphenidate extended release (XR) or placebo found that dexmethylphenidate XR resulted in improvement in ADHD Rating Scale scores from baseline to 5 weeks, and that all doses of dexmethylphenidate XR achieved greater responses than placebo.³²

Common adverse effects associated with methylphenidate are typical of any stimulant, and include nervousness and insomnia.³³ In adults, OROS methylphenidate is associated with an increase in blood pressure and heart rate; common adverse events in adolescents include headache, insomnia, and accidental injury.³¹ Adverse effects associated with dexmethylphenidate include dry mouth, headaches, and anxiety.³² Nevertheless, these formulations are all reasonably well tolerated, and patients can achieve meaningful symptom improvement if doses of 1 to 2 mg/kg can be reached.³¹⁻³³

Amphetamine. As with methylphenidate, the safety and efficacy of mixed amphetamine salts (MAS) has been supported by clinical research. Spencer et al performed a 7-week, randomized, double-blind, placebo-controlled, crossover study of a MAS compound in the treatment of adult ADHD. Drug-specific improvement in ADHD symptoms was significant, with a 42% decrease on the ADHD Rating Scale ($P<.001$), and the percentage of subjects taking MAS who improved was considerably higher than those on placebo (70% vs 7%; $P=.001$).³⁴

Similarly, the extended-release form of MAS (MAS-XR) has also been proven safe and effective. A 24-month, open-label extension of a 4-week, double-blind, placebo-controlled study found that improvements in ADHD symptoms occurred in all 223 subjects and were sustained for 24 months.³⁵

Dextroamphetamine is another effective option for the pharmacologic treatment of adult ADHD. A randomized, double-blind, placebo-controlled study found that subjects receiving the drug demonstrated a greater therapeutic response than those on placebo.³⁶

The most common adverse effects associated with MAS and MAS-XR include dry mouth, loss of appetite, insomnia, and headache.³⁷ Dextroamphetamine is associated with elevated blood pressure, dry mouth, headache, and weight loss.³⁸ Adverse effects are common, and are dependent upon both dose and blood level; titration of the medication typically alleviates these effects.

Atomoxetine. Atomoxetine, a highly selective inhibitor of the norepinephrine transporter, has been proven to reduce symptoms of ADHD in adults. Faraone et al analyzed data from 2 double-blind, placebo-controlled, parallel-design studies of adult ADHD patients who were randomized to 10 weeks of treatment with atomoxetine or placebo. Atomoxetine patients were more likely to show a reduction in ADHD symptoms than those receiving placebo, and atomoxetine prevented a worsening of most symptom classes.³⁹

The most common adverse effects associated with atomoxetine include dry mouth, headache, insomnia, and nausea.⁴⁰ Rare cases of liver damage have been reported with atomoxetine use; therefore, patients should be monitored closely for symptoms using periodic liver function tests.⁴⁰

TABLE 4

Patient Health Questionnaire 9²⁶

- Little interest or pleasure in doing things
- Feeling down, depressed, or hopeless
- Trouble falling or staying asleep, or sleeping too much
- Feeling tired or having little energy
- Poor appetite or overeating
- Feeling bad about yourself—or that you are a failure or have let yourself or your family down
- Trouble concentrating on things, such as reading the newspaper or watching television
- Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual
- Thoughts that you would be better off dead, or of hurting yourself in some way

General Precautions for Stimulants and Atomoxetine. In general, adult ADHD patients treated with a stimulant or atomoxetine should be observed for serious cardiac events and evaluated for cardiac abnormalities prior to beginning treatment.^{32,33,37,38,40} Because psychiatric adverse events are possible, clinicians should use caution when prescribing stimulants or atomoxetine to patients with preexisting psychosis, such as bipolar disorder; furthermore, patients should be observed carefully for emergence of new symptoms of psychosis or change in mood.^{32,33,37,38,40}

Concurrent Treatment. Concurrent treatment for comorbid adult ADHD and MDD is currently under investigation. To date, few studies have been published examining concurrent treatment with concrete results. Data are still needed regarding both the safety and efficacy of concurrent treatment and the impact of long-term concurrent treatment of ADHD and MDD on patient outcomes.

Conclusion

The prevalence of ADHD in the adult population is significant, with high rates of underrecognition and underdiagnosis. Inattention, the predominant symptom type in adults, persists over time and is associated with broad areas of dysfunction, and is, therefore, the main target for treatment. Adult ADHD overlaps considerably with MDD, as 9.4% of patients with MDD have adult ADHD, and 18.6% of patients with adult ADHD also have MDD.⁹ Screening for ADHD and MDD concomitantly, selecting appropriate combination therapy to target both conditions, and tracking patient response over time using systematic rating scales can improve outcomes for individuals with these comorbid psychiatric conditions. ■

CASE STUDY

Diagnostic Prioritization of Comorbid ADHD and Dysthymia

Based on a presentation by David W. Goodman, MD, Director, Adult Attention Deficit Disorder Center of Maryland, Johns Hopkins at Green Spring Station

Case Description A 39-year-old stay-at-home mother of 2 requests an attention-deficit/hyperactivity disorder (ADHD) evaluation after noticing similarities between her own behavior and that of her 8-year-old son, who was recently diagnosed with ADHD. The patient reports acting impulsively; in particular, her impulsive spending has led her to incur substantial debt, forcing her husband to take away her credit cards. She is easily distracted, has had several automobile accidents, and has totaled the family car 3 times. The patient also complains of chronic dysthymia, which has persisted for 6 years. The patient and her husband agree that her symptoms have placed a great deal of strain and stress on the marriage and family.

Case Discussion The patient was diagnosed at 33 years of age with moderate postpartum depression following the birth of her second child. She received counseling and unsuccessful trials of the selective serotonin reuptake inhibitors paroxetine and sertraline and the monoamine oxidase inhibitor phenelzine. She has not returned for treatment of her chronic dysthymia because she was demoralized by the lack of response to antidepressants.

The patient's early history is indicative of undiagnosed ADHD. Retrospectively, the patient says she was described by teachers as inattentive and was often told that she needed to focus and listen more carefully. Her mother also reported that the patient was impulsive, sometimes damaging others' property, and was accident-prone due to distractibility.

The patient's family history is likely positive for ADHD. Her father has a history of impulsive and disruptive behavior leading to frequent job changes and firings. Her brother has had similar job-related difficulties, and cannot find work that holds his interest. However, neither the patient's father nor brother have been formally diagnosed with ADHD.

In addition to a complete history and interviews with the patient's adult family members with suspected ADHD, a diagnosis of ADHD in the patient should be confirmed clinically through the use of interview tools and rating scales. While several scales are available for diagnosis, one should be selected and used consistently throughout the course of treatment to determine the patient's response to care.

The central challenges in this case are deciding which psychiatric condition to treat first—chronic dysthymia or ADHD—and determining an appropriate pharmacologic sequence for treatment. Diagnostic prioritization of the patient is required to develop a sequential pharmacologic algorithm.¹ The goal of treatment will be to improve one disorder without making the comorbid disorder worse.¹

Current recommendations for diagnostic prioritization in patients with adult ADHD and psychiatric comorbidity specify the following order of treatment:¹

1. Alcohol and substance abuse
2. Mood disorders, including bipolar disorder and major depression
3. Anxiety spectrum disorders, such as obsessive-compulsive disorder and panic disorder
4. ADHD

The recommendation that ADHD be treated last is based on 2 considerations. First, the cognitive difficulty experienced by adults with ADHD may be produced by the aforementioned diagnoses. Second, the stimulant medications used in ADHD treatment may exacerbate psychiatric comorbidities. However, in the context of this scheme for diagnostic prioritization, the clinician must also consider the relative severity of the concurrent disorders.¹ For example, if the clinical evaluation reveals that the patient has severe ADHD, but only mild dysthymia, she may first be treated for the ADHD to determine the impact of treatment on dysthymia symptoms. However, if the patient presents with frank major depression and ADHD, then the depression should be treated first, as some of the cognitive difficulties may be secondary to the depression.

Given that the patient's symptoms are causing considerable impairment, a trial of pharmacotherapy and/or psychotherapy is warranted. Optimal pharmacologic treatment for adult ADHD will reduce the frequency and/or severity of ADHD symptoms over the course of the day while minimizing the number of times the medications need to be taken. This patient does not have any concurrent medical disorders or potential substance abuse issues that must be considered prior to prescribing pharmacotherapy.

The 3 pharmacologic options to consider include stimulant medication, nonstimulant medication, or an antidepressant for the patient's chronic dysthymia.

“If the clinical evaluation reveals that the patient has severe ADHD, but only mild dysthymia, she may first be treated for the ADHD to determine the impact of treatment on the dysthymia symptoms.”

In the stimulant category, the patient might be given a once-per-day long-acting medication or a short-acting, multiple dose agent. The Food and Drug Administration (FDA) has approved 2 stimulant medications for the treatment of adult ADHD: extended-release mixed amphetamine salts or dexamethyl phenidate extended release.²

The second option is treatment with a nonstimulant. The FDA has approved atomoxetine for the treatment of adults with ADHD; bupropion, an unapproved agent, or another agent such as an alpha agonist might also be an option. These agents might be considered for a number of reasons, including suspicion of patient abuse of stimulant medications, a history of poor tolerance of stimulants, or potential adverse effects or interactions of stimulants with other medical conditions diagnosed in the patient; for example, the use of stimulants could exacerbate blood pressure or may be contraindicated in an individual with specific cardiac issues.

The third possibility is to treat the patient with an antidepressant to address the chronic dysthymia and then consider ADHD treatment depending upon symptom response. This regimen could include bupropion, which might address symptoms of both conditions, or another antidepressant, such as a tricyclic antidepressant, a selective serotonin reuptake inhibitor, or a serotonin-norepinephrine reuptake inhibitor.

The effectiveness of medical therapy for patients with adult ADHD and a psychiatric comorbidity is often enhanced by psychotherapy. Psychotherapeutic options include cognitive behavioral therapy, which has been recently shown to be highly effective in ADHD patients, especially when used concurrently with medication.³ Historically, cognitive behavioral therapy has been proven to be highly effective for depression. Additional psychotherapeutic strategies include organizational therapy for the patient and her family as well as regular adult ADHD coaching services. ■

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EXPERT INTERVIEW

Q&A session with William W. Dodson, MD, David W. Goodman, MD, and Andrew A. Nierenberg, MD

Q *How often should clinicians in the outpatient sector who are treating patients for comorbid ADHD/MDD utilize rating scales to determine an objective level of symptom improvement?*

A **Dr. Nierenberg:** I am a proponent of regularly performing rating scales across all of the psychiatric disorders that I treat. I routinely ask patients to complete the relevant rating scales every time they come in, and then share the results of those rating scales with the patient. This allows patients to more easily see their improvement over the course of treatment, so that they can concretely track how their treatment has affected them over time.

Dr. Goodman: I think the rating scales are important for a number of reasons. First, they give you a quantification of very specific symptoms from the patient's perspective rather than the clinical interview, which usually results in broader responses by the patient. Also, sometimes during the clinical interview, patients will minimize symptoms, but they will indicate a more realistic response via the rating scale.

Using a rating scale, you can show patients who decide to go on and off medication or who change medication what their ratings were over the course of time, since their ability to recall history may not be accurate. It is often very helpful for patients to see their score on the ADHD Rating Scale was 45 when they came in and it is now 14; it is then indisputable that the treatment was very helpful.

Q *Are there any recommended nonpharmacologic treatment options for ADHD?*

A **Dr. Goodman:** First, we really should remember that there is an enormous amount of research speaking to the fact that stimulant medications, specifically, and the medications approved for ADHD in general, are highly effective. If you look at the effect sizes for stimulant medications, they are among the highest—if not the highest—and the most effective psychotropic medications we have for any psychiatric condition.

When we speak about nonpharmacologic interventions, my hope is that we speak about them in concert with medications. Ideally, these interventions would be used adjunctively, or in a complementary fashion to pharmacotherapy, not as an alternative to therapy. But if you have a patient with adult ADHD, with or without MDD, and they say, "I absolutely refuse to take any medication, what else can you offer me?" there are a number of therapies that are helpful—although they will be less effective without medication than they would be in conjunction with medication—including organizational techniques, such as time management, for someone who has strong executive dysfunction. Cognitive behavioral therapy is specifically used to help patients who are demoralized or dysthymic due to frustration they feel at their perceived inability to get things accomplished. We also teach family members—spouses in particular—how to best present and organize information in the household so that they do not grow increasingly frustrated or exhausted with having to repeat themselves for the untreated ADHD individual.

Ideally, these strategies would be employed for a short period of time, after which the patient would move on to an empiric trial of medication. In this instance, I would tell the patient that he or she does not have to take the medication for a lifetime. He or she can take it for a month, and if it changes how he or she is functioning, the patient will make the decision—does he or she want the quality of life on medicine, or the quality of life off medicine?

Dr. Nierenberg: Some people have also looked at biofeedback and the evidence, as far as I know, is equivocal at best.

Dr. Goodman: Biofeedback and exercise have been examined, as well as herbal preparations, all of which show some limited benefit. It is the sustainability of that benefit that is highly questionable. For example, exercise can improve cognition for the time after exercise but unless a patient is going to exercise every 6 hours, I am unsure how effective it is over a long period of time. And that really is important—the efficacy of a treatment in a short period of time does not necessarily mean that the treatment can sustain its benefit over a long period of time.

Q *The results of a recent study compared long-acting ADHD stimulant medications with short-acting stimulant medications and suggested that the fluctuations in blood levels were perhaps beneficial in treating ADHD, compared with the constant level attained with longer-acting medications. Can you comment on that?*

A **Dr. Dodson:** In our clinic we do not use short-acting or immediate-release products. With the more complicated dosing schedule, these agents give a very forgetful population another opportunity to forget. The patient comes in looking for stability of engagement, performance, impulse control, and mood. Things that do not provide stability undermine the fundamental goal of medication treatment. The idea that you need an ascending curve is inaccurate—you need an ascending curve in order to get stimulation, but not to get benefit for ADHD symptoms. With the immediate-release medications, there is no advantage over the extended-release formulation, and there are a lot of disadvantages with frequent dosing, including poor compliance and the risk of rebound adverse effects between doses. ■

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