Attention deficit hyperactivity disorder in adults: Treatment overview

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Literature review current through: **Oct 2023.**
This topic last updated: **Aug 10, 2023.**

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD), one of the most common neuropsychiatric disorders of childhood and adolescence, often persists into adulthood [1]. Studies have found that a majority of people diagnosed with ADHD in childhood continue to be significantly impaired as adults [2,3]. ADHD in adulthood is associated with significant impairment in occupational, academic, and social functioning.

Findings from clinical trials of medications for ADHD in adults echo many of the findings on effective medications in child/adolescent ADHD; however, these data are less extensive in adults compared with children, show greater variability in outcomes, and have generated less definitive information on medication efficacy and dosing [1,2].

This topic and two algorithms (algorithm 1 and algorithm 2) describe our management of ADHD in adults. The epidemiology, pathogenesis, clinical manifestations, assessment, diagnosis, and psychotherapy of adult ADHD are reviewed separately. Topics related to ADHD in children and adolescents are also reviewed separately.

- (See "Attention deficit hyperactivity disorder in adults: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Attention deficit hyperactivity disorder in adults: Psychotherapy".)

- (See "Attention deficit hyperactivity disorder in children and adolescents: Overview of treatment and prognosis".)
- (See "Attention deficit hyperactivity disorder in children and adolescents: Epidemiology and pathogenesis".)
- (See "Attention deficit hyperactivity disorder in children and adolescents: Clinical features and diagnosis".)
- (See "Attention deficit hyperactivity disorder in children and adolescents: Treatment with medications".)
- (See "Pharmacology of drugs used to treat attention deficit hyperactivity disorder in children and adolescents".)

INITIAL TREATMENT

Preference for combination medication and CBT — We suggest first-line treatment with a combination of medication and cognitive-behavioral therapy (CBT) targeting executive dysfunction for most adults diagnosed with attention deficit hyperactivity disorder (ADHD). This is particularly true in individuals with severe executive dysfunction (algorithm 1 and algorithm 2). (See "Attention deficit hyperactivity disorder in adults: Psychotherapy", section on 'Overview of management of ADHD in adults'.)

Both stimulant medication [4-7] and CBT [8-10] have been reported to be effective treatments for ADHD in adults. However, there have been no clinical trials in adults directly comparing the efficacy of CBT and medication separately and in combination. Therefore, we rely on studies that conducted these comparisons separately. Medication clearly augmented the benefit of CBT in one randomized, controlled, adequately powered study [11]. Five studies have assessed the benefits of adding CBT to medication, with four studies reporting positive results [12-15] and one study reporting negative results [16]. However, none of these studies included a control for non-specific effects of psychotherapy. Nevertheless, these results strongly suggest that the combination of stimulant medication and CBT is better than either treatment alone.

As examples:

- In a trial, 88 adults with ADHD were randomly assigned to 12 manualized group sessions either with (n = 42) or without (n = 46) stimulant medication [11]. At treatment end and three months, subjects in the treatment group (CBT and stimulant) showed greater improvement on observer-reported and self-reported scales than subjects in the CBT-only group. However, at six months, while both groups maintained gains, the difference in treatment effects lessened and were similar in overall improvement.

- In another trial, 95 adults with ADHD who were being treated with medication were randomly assigned to treatment as usual or 15 sessions of CBT [12]. At treatment end, subjects who received CBT experienced reduced ADHD symptoms (eg, Kiddie-Schedule for Affective Disorders and Schizophrenia [ADHD section], Clinical Global Impression scale, Barkley Current symptoms scale) as compared with the group receiving treatment as usual. This difference was maintained at three months. The effect size was noted to be modest (0.55) for a trial that did not control for the nonspecific effects of psychotherapy.

However, we modify the initial treatment for specific populations such as individuals with substance use disorder (SUD) or other co-occurring disorders. (See 'Initial treatment for specific populations' below.)

Additionally, for individuals with contraindications to medication, or in those who prefer not to take medication or engage in CBT, we use the patient preferred treatment as monotherapy. (See "Attention deficit hyperactivity disorder in adults: Psychotherapy".)

Stimulants as preferred pharmacologic treatment — For most adults with ADHD, we suggest first-line pharmacologic treatment with a stimulant medication (eg, amphetamines or methylphenidate) rather than nonstimulant medications such as atomoxetine or antidepressants. An advantage of stimulant medication is that they have a clinical effect almost immediately after starting, while atomoxetine and the antidepressants have a delayed onset of full therapeutic action of up to four weeks, related both to the titration of the medication and the delay in the onset of action of the agent [17].

There are no direct comparisons between stimulant and nonstimulant medications in clinical trials. Meta-analyses have shown that effect sizes in short-term trials of adult ADHD are greater for stimulants compared with nonstimulant medications, including atomoxetine and atypical antidepressants (bupropion, tricyclic antidepressants [TCAs], and venlafaxine) [4-7]. As an example, in a meta-analysis of 11 trials including 1991 adults with ADHD, pooled effect size for stimulants was somewhat greater versus placebo than for nonstimulant medications (Cohen's d = 0.67 versus 0.59, respectively) [5].

A table on medications for adult ADHD describes their dosing, onset of action, and duration of effects (table 1).

Choosing a stimulant — Among the stimulant medications, our first choice is typically an amphetamine rather than methylphenidate. Within each of these groups there are various formulations without established superiority in efficacy. Our choice is based on the properties of the medication (eg, half-life, time to onset) and prescriber familiarity and preference.

- **Amphetamines** – Amphetamine stimulants include dextroamphetamine and lisdexamfetamine, and can be short- or long-acting [18]. Amphetamine medications for ADHD are available in immediate- and extended-release formulations and have an onset of action of 20 to 60 minutes. The immediate-release formulation of dextroamphetamine-amphetamine has a duration of up to 6 hours [19,20]. Longer-acting formulations may last up to 10 to 12 hours [19-22].

- **Methylphenidate/dexmethylphenidate** – Methylphenidate stimulants contain dexmethylphenidate or racemic mixtures of methylphenidate [21,23,24] and are either short-acting (3 to 5 hours), intermediate-acting (4 to 8 hours), or long-acting (8 to ≥12 hours). In addition to oral formulations, a methylphenidate patch is available and should be applied two hours before needed because of a delay in the onset of clinical effects.

While amphetamines and methylphenidate have long been considered comparably efficacious for adult ADHD, some data appear to show a benefit of amphetamines in reducing core symptoms of ADHD (eg, inattention, impulsivity, hyperactivity) compared with methylphenidate. In a network meta-analysis of 51 medication trials including 8131 adults with ADHD, after 12 weeks of treatment, individuals treated with amphetamines showed greater effect on clinician rating scales of overall ADHD symptoms than methylphenidate (standardized mean difference -0.29, 95% CI -0.54 to -0.05) [7]. However, amphetamines were associated with higher risk of treatment ending early as the result of adverse events. No differences in efficacy were seen between higher and lower doses of amphetamines.

Long- versus short-acting stimulants — Our choice of stimulant preparation is based on the patient's preference, time to onset and length of desired effect, concern about misuse or diversion, cost, and availability of the medication. Some adults value the ability to target the short-acting drugs' coverage to the desired part(s) of the day (eg, time in class or at work). Others prefer the simplicity of the longer-acting stimulant's all-day or most-of-the-day coverage (table 1).

Studies suggest that longer-acting stimulants may be less likely to be abused or diverted [25-27]. A lower abuse potential for long-acting compared with short-acting stimulants is based on studies demonstrating greater subjective responses and potential reinforcement for immediate-release stimulants compared with extended-release methylphenidate in healthy adults [27].

Despite pharmacologic and pharmacokinetic differences in stimulants used to treat adult ADHD, there does not appear to be differences in efficacy between short- and long-acting stimulants [4,7].

Pretreatment evaluation and contraindications — Prior to initiating treatment with a stimulant in adults, we review their cardiovascular history including history of chest pain, palpitations, syncope, myocardial infarction, arrhythmia, valvular disease and their family history.

We measure blood pressure and pulse in all patients and obtain an electrocardiogram (ECG) in individuals with cardiac history or cardiac symptoms such as palpitations or chest pain. In individuals with a cardiac history, or when findings are outside of normal limits are seen, we consult with a cardiologist to determine whether the findings are sufficiently severe to avoid these medications [28].

Dose and titration — We typically begin treatment with a low dose of the chosen agent and increase weekly while monitoring for clinical response, duration of the effect during the day, and side effects (table 1). (See 'Monitoring' below and 'Defining response' below.)

As examples:

- For short-acting dextroamphetamine-amphetamine, we begin at 5 mg orally in the morning on the first day. If tolerated, we increase to 5 mg twice a day (approximately at breakfast and lunch; eg, four hours between doses) beginning on the day 2 to 7. We monitor for improvement (see 'Monitoring' below) in symptoms for one week. If adequate improvement is not seen, we increase by 5 mg at weekly intervals until clinical response is adequate, intolerable adverse effects limit further titration, or maximum total daily dose limit reached (60 mg).

- For short-acting methylphenidate, we typically begin with 10 mg orally in the morning. If initial dose is tolerated, we increase to 10 mg at breakfast and lunch each day on day 2 to 7. Depending on response to medication, we increase by 10 mg at weekly intervals until clinical response is adequate, adverse effects limit further increases, or maximum daily dose is reached (60 mg).

- For long-acting dextroamphetamine-amphetamine (mixed salts), we typically begin at 10 mg orally each morning. If there are no adverse effects after three or four days, we increase to 20 mg once per day in the morning. We increase by 10 mg at weekly (or longer) intervals until clinical response or a dose of 40 mg per day is reached. Doses above 40 mg per day are rarely necessary and require close monitoring.

Benefits of stimulant treatment

- **Symptomatic improvement** – Stimulant medications have been shown to offer symptomatic improvement (particularly in attention and on-task behaviors) as well as improvement in daily functioning (vocational and interpersonal performance) in adults as compared with placebo [5,7,18,29-32].

  As examples, in a meta-analysis of trials, 1100 adults with ADHD were randomly assigned to receive stimulant medications or placebo for up to 12 weeks [5]. Participants who received stimulants experienced greater improvement in ADHD symptoms compared with placebo, with an estimated effect size in the medium to high range (Cohen's d = 0.67). Another systematic review identified four trials in adults with ADHD that suggested potential improvement in investigator- or participant-reported symptoms with methylphenidate compared with placebo, although the evidence was of very low certainty [30]. (See "Attention deficit hyperactivity disorder in adults: Epidemiology, clinical features, assessment, and diagnosis", section on 'Clinical manifestations'.)

- **Driving and work performance** – Although evidence of positive effects on long-term psychosocial outcomes is limited, observational studies have found benefits from stimulant medication on functioning, self-esteem, and work performance [33]. Additionally, while previous studies have found that individuals with ADHD are more likely to be involved in a motor vehicle collision compared with individuals without the disorder, treatment of ADHD with medications lowers the risk of collisions [34,35]. A cohort study of 2,319,450 patients diagnosed and treated for ADHD in the United States compared the risk of a motor vehicle collision in ADHD patients during months when they were and were not receiving ADHD medication [36]. Males and females had a lower risk of a collision when receiving ADHD medication, by 38 percent (odds ratio 0.62, 95% CI 0.56-0.67) and 42 percent (odds ratio 0.58, 95% CI 0.53-0.62), respectively. (See "Attention deficit hyperactivity disorder in adults: Epidemiology, clinical features, assessment, and diagnosis", section on 'Clinical manifestations'.)

- **Duration of effect** – Clinical trials have primarily focused on short-term effects (eg, 12 weeks) of stimulant medications. These trials have consistently shown positive short-term effects.

  Examples of clinical trials investigating the short-term effects of stimulants include:

  - **Amphetamines** – In a trial, 255 adults with ADHD were randomly assigned to treatment with mixed amphetamine salts extended-release at dose of 20 mg, 40 mg, 60 mg, or placebo over four weeks [29]. Improvement in symptoms based on the ADHD-Rating Scale were shown at each of the three doses respectively versus placebo.

- **Methylphenidate** – In a meta-analysis of 16 trials including 3799 subjects with ADHD, individuals treated with extended-release methylphenidate showed greater improvements in self-rated ADHD symptoms as compared with placebo (standardized mean difference -0.37, 95% CI -0.43 to 0.3) [31]. Additionally, improvements as compared with placebo were noted in self-rated quality of life (standardized mean difference -0.15, 95% CI -0.25 to -0.05; six trials, 1888 participants), investigator-rated ADHD symptoms (standardized mean difference -0.42, 95% CI -0.49 to -0.36; 18 trials, 4183 participants), and family- or peer-rated ADHD symptoms (standardized mean difference -0.31, 95% CI -0.48 to -0.14; three trials, 1005 participants). Treatment with extended-release methylphenidate was no better than placebo on "missed days at work." All outcomes were rated as very low-quality evidence.

  In another six-week trial, individuals treated with methylphenidate were more likely to experience a 30 percent or more decline in symptoms versus those treated with placebo (68 versus 17 percent) [37].

Longer-term data on the efficacy of stimulants in adult ADHD are limited in amount and quality. Results from trials and observational studies suggest that continued stimulant treatment may lead to sustained improvement in ADHD symptoms for at least 24 to 52 weeks. For example:

- In a 24-week trial, 359 individuals with ADHD were randomly assigned to receive either extended-release methylphenidate (mean dose 0.55 mg/kg) or placebo. A greater proportion of individuals treated with active medication experienced a 30 percent relative improvement in ADHD symptoms as compared with individuals treated with placebo (61 versus 42 percent) [23].

- In an uncontrolled follow-up study, 96 adults with ADHD who improved while taking methylphenidate in randomized trials reported sustained improvements in ADHD symptoms at 30 weeks with continued medication [38].

- In another uncontrolled follow-up study, 78 individuals who had improved in response to immediate release methylphenidate showed ongoing improvements in ADHD symptoms and psychosocial functioning at one year [24].

Adverse effects — Stimulant medications are generally well tolerated when taken as directed. Side effects of stimulants reported in adults treated for ADHD include dry mouth, insomnia (particularly if the duration of medication effects extends into the evening or if the medication is taken late during the day), irritability, dysphoria, diminished appetite, weight loss, and headaches [39]. Nontherapeutic effects such as euphoria or elevated mood may lead to misuse

of medications. Additionally, exacerbation of existing motor and vocal tics, as well as new onset of tics, has occurred. In a meta-analysis of clinical trials, 10 percent of adults with ADHD treated with stimulant medications discontinued the medication due to adverse events [40].

Other effects that may be seen in individuals treated with stimulant medications include:

- **Psychosis** – Psychosis has been reported in individuals who misuse or take excessive amounts of stimulant medication and may be an indication that a stimulant is being misused. Additionally, psychosis may be seen in individuals with a vulnerability to psychosis (eg, comorbid schizophrenia, schizotypal personality disorder, mood disorders with psychosis, history of amphetamine induced psychosis) [41]. Otherwise, psychosis appears to be rare in clinical samples of adults with ADHD receiving stimulant treatment.

  In a study of data from national registries in Sweden, treatment-emergent mania was found to be associated with the initiation of methylphenidate treatment in adults with co-occurring bipolar disorder and ADHD; however, this association was seen only in patients who were not taking a mood stabilizing medication [42]. (See 'Bipolar disorder' below.)

- **Cardiovascular effects** – Consistent elevations in systolic and diastolic blood pressure (3 to 5 mmHg) and heart rate (five beats per minute) have been reported to result from stimulant treatment of ADHD in adults. The increases appear to be correlated, in part, to dose [43]. Longer-term data on the cardiovascular effects of these medications in adults suggest that these effects do not diminish over time. Research on the relationship between treatment with stimulants and serious cardiac events has found mixed results:

  - In a meta-analysis of observational studies, an association between treatment for ADHD with stimulant or nonstimulant medications and the risk of cardiovascular disease (ie, hypertension, ischemic heart disease, cerebrovascular disease, heart failure, venous thromboembolism, tachyarrhythmias, and cardiac arrest) across age groups was not supported [44]. Pooled adjusted relative risks between ADHD medication use and any cardiovascular disease was 1.04 (95% CI 0.43-2.48; (seven studies, n >850,000) and 1.59 (95% CI 0.62-4.05; six studies, n >267,000 subjects) in young/middle-aged adults and older adults, respectively.

  - A retrospective analysis of 43,999 patients newly treated with methylphenidate, matched to nonusers of methylphenidate, found a 1.8-fold increase in sudden death or ventricular arrhythmia. The absence of a dose-response relationship suggested that the association between the medication and cardiac events may not be causal [28].

- A retrospective, population-based cohort study of over 150,000 patients treated with methylphenidate, amphetamine, or atomoxetine did not find an association between stimulant treatment and the risk of sudden cardiovascular events among young and middle-aged adults [45].

- **Priapism** – Priapism is a rare complication of methylphenidate stimulants in adult males, adolescents, and boys [46-48]. Fifteen cases with a median age 12.5 years (range 8 to 33 years) were reported to the US Food and Drug Administration over a 15 year period [49]. Two cases required surgical treatment. Priapism has also been reported among four patients taking amphetamine stimulants [49]; causation is uncertain as these patients were taking other medications thought to cause priapism. The diagnosis and treatment of priapism are discussed in a separate topic. (See "Priapism".)

- **Potential for misuse or addiction** – Prescription stimulants are subject to misuse, dependence, and/or diversion. Misuse of prescription drugs, including stimulants, is reviewed in detail separately. (See 'Substance use and alcohol use disorder' below and "Prescription drug misuse: Epidemiology, prevention, identification, and management".)

  In studies of adults receiving stimulants for ADHD, stimulant treatment does not appear to affect the likelihood of subsequent SUD development, neither increasing SUD risk nor having a protective effect. A meta-analysis of 15 longitudinal studies that compared patients with a history of stimulant-treated ADHD to matched cohorts without stimulant treatment found no association between stimulant treatment history and subsequent substance use, abuse, or dependence [50]. In a national United States survey, 8.9 percent of the participants with a prescription for ADHD medication reported to have sold, traded, or given away their medication [51].

  However, individuals with recent or current SUDs are believed to be at higher risk of misuse [52,53]. (See "Alcohol use disorder: Treatment overview" and "Stimulant use disorder: Treatment overview" and "Opioid use disorder: Treatment overview".)

Counseling on low-risk and risky alcohol use — We caution individuals treated with stimulants for ADHD about simultaneous consumption of alcohol and stimulants. We recommend these individuals limit their alcohol use to one to two drinks after the expected therapeutic effects of the simulant have likely ended (ie, in the evening after morning stimulant administration). Prior use of alcohol may have clinically significant interactions with a number of subsequently administered stimulant drugs, including methylphenidate [54] and effects on the medications' pharmacokinetic and/or pharmacodynamic properties [54] through the production of new psychoactive metabolites [55].

Alternatives to stimulant medications

Norepinephrine reuptake inhibitors — Atomoxetine [56] and viloxazine are nonstimulant medications that inhibit reuptake of norepinephrine. These agents have minimal abuse potential and appear to be efficacious in adult ADHD; however, indirect comparison of effect sizes in clinical trials suggest that stimulant medications are more effective [4,6,7]. (See 'Stimulants as preferred pharmacologic treatment' above.)

- **Atomoxetine** – Atomoxetine is an effective medication for adult ADHD with little to no abuse potential and is not universally classified as a controlled substance [57].

  We typically begin treatment with atomoxetine at 40 mg given once daily either in the morning or evening. We increase to 80 mg daily after three or four days if the medication is tolerated. We then monitor for an additional four weeks and if the effect is not sufficient we increase to the maximum dose of 100 mg per day. If adequate improvement is not seen after another four weeks, trial of another medication is indicated.

  The most common side effects observed with atomoxetine have included dry mouth, insomnia, nausea, decreased appetite, constipation, decreased libido, erectile dysfunction, urinary hesitancy, dizziness, and sweating [58]. Aggressive behavior or hostility, and the emergence of psychosis or mania may be associated with treatment with atomoxetine [59]. In a six-month trial, patients discontinued medication treatment due to adverse events at a higher rate in the atomoxetine compared with the placebo group (17.2 versus 5.6 percent) [60].

  Atomoxetine is rapidly absorbed after oral administration. It is metabolized primarily through the hepatic cytochrome P450 system, through the 2D6 enzyme. There have been reports of hepatoxicity in two patients taking atomoxetine, with both patients recovering upon discontinuation. Atomoxetine can produce QTc prolongation in some individuals. (See "Cardiac evaluation of patients receiving pharmacotherapy for attention deficit hyperactivity disorder", section on 'Pretreatment clinical evaluation'.)

  Although there is a “boxed warning” for atomoxetine in youth under the age of 25 regarding suicidal behavior, no similar behaviors have been reported in studies of adults with ADHD.

  Analyses of multiple clinical trials have found atomoxetine, as compared with placebo, to reduce core ADHD symptoms (eg, inattention, hyperactivity) as well as improve executive functioning and quality of life in adults.

- In a meta-analysis of 12 trials including 3375 adults with ADHD, individuals treated with atomoxetine had greater reduction in core symptoms of inattention and hyperactivity/impulsivity than those treated with placebo (standard mean difference -0.33, 95% CI -0.43 to -0.23) [61]. However, the overall rate of discontinuation due to adverse effects was greater for atomoxetine than placebo (odds ratio 2.57, 95% CI 1.78-3.71).

- In an analysis of industry sponsored trials (nine trials, 3374 individuals) individuals were randomly assigned to treatment with atomoxetine or placebo [62]. Over the short term (approximately 12 weeks), the percent of atomoxetine patients meeting criteria for improvement in ADHD symptoms was greater than that achieved by patients assigned to placebo (34.8 versus 22.3 percent). In longer-term analyses (eg, six months), patients assigned to atomoxetine had a greater response rate compared with placebo (43.4 versus 28.0 percent).

  Longer-term efficacy (six months or longer) has been reported for atomoxetine, as compared with placebo, for other outcomes such as executive functioning and quality of life [60,63]. Additionally in an uncontrolled trial including 125 individuals with atomoxetine for ADHD, a mean symptom reduction of 30 percent on the Connors' Adult ADHD Rating Scale-Investigator Rated: Screening Version was maintained over a mean of 221 weeks [64].

- **Viloxazine** – Viloxazine is a nonstimulant medication that acts via selective inhibition of norepinephrine and serotonin reuptake and is approved for treatment of children and adults with ADHD [65,66]. In a trial, 50 patients (35 of them children), were treated with four weeks of atomoxetine (mean dose 60 mg/day; range 25 to 100 mg/day), followed by a five-day washout period, then treatment with Viloxazine ER (mean dose 300 mg per day; range 100-600 mg/day) [67]. After four weeks, treatment with viloxazine ER, as compared with atomoxetine, was associated with greater reduction in core ADHD symptoms, as well as fewer side effects, and a preference of 96 percent for continued treatment with viloxazine.

  We begin viloxazine at 200 mg orally once daily in adults with ADHD. We increased by 200 mg weekly to a total daily dose of 600 mg daily. For individuals with severe renal impairment (GFR <30 ml/min) we begin at 100 mg daily and titrate by 50 to 100 mg weekly to 200 mg total.

  Side effects include insomnia, fatigue, irritability, nausea, headache, elevation of blood pressure or heart rate, activation of mania or hypomania, and possible emergence of

suicidal thoughts. We monitor all adults treated with viloxazine for the emergence of suicidal thoughts or behaviors at each visit and are especially vigilant during the first few months of treatment and at times of dose changes.

Clinical experience with viloxazine is limited. In an unpublished trial, 374 adults were randomly assigned to flexible dose of viloxazine (200 to 600 mg) or placebo for six weeks [65]. At treatment end, the reduction on the ADHD Investigator Symptom Rating Scale, an 18-point measure of symptoms, was greater in adults treated with viloxazine as compared with placebo (mean difference -3.7, 95% CI -6.2 to -1.2).

Information on administration, dose, titration and adverse effects of atomoxetine and viloxazine are found on the associated table (table 1).

Antidepressant medications — Bupropion, an atypical antidepressant, and nortriptyline, a TCA, have been shown to have efficacy in adults with ADHD. We typically use them as a treatment option for adults with ADHD who have not responded to the above agents. However, we use bupropion in the treatment of individuals with co-occurring active major depression and ADHD as it has established efficacy for both disorders. (See 'Depression' below.)

- **Bupropion** – While bupropion appears to be effective for adults with ADHD, clinical effects of bupropion may take up to several weeks to appear.

  We typically give sustained release bupropion beginning at 100 mg in the morning and, if tolerated, we increase to 100 mg twice daily after one to two weeks. We maintain at this dose for three to four weeks. If adequate response is not seen at that time (see 'Monitoring' below), we increase in 100 mg increments to a maximum dose of 200 mg twice daily. We monitor at three to four weeks after each dose increase. Bupropion extended-release is given once daily beginning at 150 mg. We increase after several weeks depending on response to 300 mg per day and then 450 mg per day given once daily. We prefer to use the extended-release formulation, as it results in a smoother delivery and lower peak level making side effect of seizure less likely.

  A meta-analysis of five randomized trials with a total of 349 adult participants with ADHD found that bupropion led to a higher response rate (relative risk 1.67, 95% CI 1.23-2.26) and a greater reduction in inattentive and overall ADHD symptoms compared with patients receiving placebo [68]. The rate of trial discontinuation (overall and due to adverse drug effects) did not differ between groups. In another trial, 162 adults with ADHD were randomly assigned to receive eight weeks of up to 450 mg/day of bupropion extended-release or placebo [69]. Individuals in the treatment group had a higher rate of response (defined as 30 percent reduction in investigator-rated ADHD symptoms) than

those in the placebo group (53 versus 31 percent). Bupropion was reported to be well tolerated with no serious or unexpected adverse effects and low rate of discontinuation (5 percent).

There are no direct comparisons of stimulant and bupropion treatment in adult ADHD; comparison of effect sizes from placebo-controlled trials of the drugs suggests that stimulants lead to greater symptom reduction compared with bupropion [70]. The efficacy of bupropion in the treatment of depression and for smoking cessation favors the use of the drug in adults with ADHD and one or both of these conditions.

Side effects of bupropion include dry mouth, nausea, insomnia, dizziness, anxiety, dyspepsia, sinusitis, and tremor. Bupropion may increase the risk of seizures, particularly with higher doses and shorter-acting formulations and in patients with eating disorders [71].

- **Tricyclic antidepressants** – TCAs appear to be efficacious in adult ADHD [72]. In our clinical experience; however, TCAs are less effective than stimulants and more poorly tolerated than stimulants, atomoxetine, or bupropion.

  With the paucity of data regarding TCAs for the treatment of adult ADHD, dosing is not well established. We typically start at a low dose and increase gradually. As an example, we begin nortriptyline at 10 mg daily and increase in 25 mg increments weekly until a therapeutic range is reached (50 to 150 ng/ml). We check therapeutic levels and assure that the individual has a three- to four-week trial at each dose within the therapeutic range. If further increases are needed (eg, due to lack of response), we continue to increase the dose until maximum therapeutic dose is reached (ie, 150 ng/ml), side effects limit further increases, or acceptable response is achieved (table 1).

  In a trial, 41 adults with ADHD were randomized to receive a six-week trial of desipramine (target dose 200 mg) or placebo [72]. At treatment end, a greater proportion of individuals in the desipramine group responded as compared with placebo (68 versus 0 percent). A small number of patients responded to a dose less than 100 mg/day; the majority required higher dosing, to a target dose of 200 mg/day for efficacy.

  Benefits of TCAs treatment include their effectiveness in treating co-occurring depression or anxiety with ADHD, lack of abuse liability, and single daily dosing. However, TCAs have greater side effects as compared with other medications that are effectively used in the treatment of ADHD. Additionally, TCAs may be lethal in overdose. Clinical trials comparing their efficacy have not been conducted.

Due to potential cardiovascular effects (eg, hypotension, hypertension, tachycardia, QTc prolongation) and cardiotoxicity of TCAs, we check ECG at baseline and at each dose increase as well as every four to six months during maintenance treatment. Although plasma levels of TCAs do not appear to be related to efficacy, monitoring plasma levels at higher doses may help to avoid toxicity or overdose. Risks of cardiotoxicity, particularly with overdose, should prompt careful monitoring of TCA treatment. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)

INITIAL TREATMENT FOR SPECIFIC POPULATIONS

Co-occurring disorders — We generally address comorbid disorders concurrently with attention deficit hyperactivity disorder (ADHD) treatment. However, in some disorders, such as active substance use disorder (SUD), we often address the co-occurring disorder prior to treating ADHD. (See "Attention deficit hyperactivity disorder in adults: Epidemiology, clinical features, assessment, and diagnosis", section on 'Comorbidity'.)

Substance use and alcohol use disorder — Polysubstance use is common in adults with ADHD [73]. While there are few reports of severe health consequences due to acute co-administration of alcohol and stimulants, some studies have documented that that administration of stimulants in conjunction with alcohol use results in potential risks beyond the additive respective behavioral effects of the substances [73].

Active substance use disorder — For individuals with active SUD, we treat the co-occurring SUD until stabilized prior to treating ADHD [73].

However, clinical trials of stimulant treatment in ADHD patients with an active co-occurring SUD (nicotine, cocaine, and opioid dependence) have found mixed efficacy results [74-78]. As an example, a clinical trial in 126 adults with both ADHD and cocaine use disorder randomly assigned patients to receive extended-release dextroamphetamine-amphetamine (60 or 80 mg/day) or placebo [74]. More patients achieved at least a 30 percent reduction in ADHD symptom severity in the 60 and 80 mg/day medication groups compared with placebo (75.0 and 58.1 versus 39.5 percent). The odds of a cocaine-negative week were higher in the 80 and 60 mg/day groups (odds ratios 5.46 and 2.92, respectively) compared with placebo.

History of substance use disorder — To avoid the risks of misuse, addiction, or diversion of prescribed stimulants in adults with ADHD and a history of SUD, we suggest first-line treatment with atomoxetine, a nonstimulant medication that inhibits presynaptic norepinephrine reuptake. Atomoxetine is effective for adult ADHD compared with placebo [61]

and has been used safely in patients with co-occurring ADHD and an SUD [79,80]. Atomoxetine has little to no abuse potential [57]. Viloxazine, a nonstimulant medication with similar properties is an acceptable alternative (algorithm 1). (See 'Alternatives to stimulant medications' above.)

Depression — We typically treat individuals with comorbid major depressive disorder with bupropion, an antidepressant with established efficacy for both disorders [68]. Subsequent treatment of individuals with comorbid depression and ADHD who do not respond to bupropion may be found below and in the associated algorithm (algorithm 2). (See 'For co-occurring disorders' below.)

There are no clinical trials comparing the efficacy of medication treatments for co-occurring depression and ADHD in adults. Information on dosing bupropion is described in a table (table 1). Administration, pharmacology and side effects of bupropion for depression can be found elsewhere. (See 'Antidepressant medications' above and "Atypical antidepressants: Pharmacology, administration, and side effects", section on 'Bupropion'.)

Anxiety disorders — We typically treat individuals presenting with ADHD with comorbid anxiety disorder (eg, generalized anxiety disorder or social anxiety disorder) with the combination of a stimulant [5] and a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) [81]. We typically address the anxiety first by starting the SSRI or SNRI, and when the anxiety has improved we add a stimulant medication (algorithm 2). (See 'Choosing a stimulant' above.)

The combination of a serotonergic medication with a stimulant can lead to excessive serotonin activity. We monitor individuals treated with the combination of serotonergic reuptake inhibitor and stimulant for the presence of serotonin syndrome, a potentially life threatening syndrome caused by excessive serotonin activity. Separate topics discuss stimulants, SSRIs, and SNRIs, as well as the serotonin syndrome. (See "Generalized anxiety disorder in adults: Management", section on 'SRIs as preferred initial therapy' and "Pharmacotherapy for social anxiety disorder in adults", section on 'Monotherapy'.)

There are no clinical trials comparing efficacy among medication treatments for co-occurring anxiety disorders and ADHD in adults.

Bipolar disorder — In individuals with comorbid ADHD and bipolar disorder, we stabilize the mood symptoms (eg, mania, hypomania) and establish therapeutic levels of mood stabilizing medication prior to treatment for ADHD [82]. The risk of precipitation of manic symptoms in individuals treated with stimulant medications appears to be attenuated by having a stable bipolar status and being on mood stabilizing medications. In a retrospective analysis of data

from the Sweden's national health registries, adults with bipolar disorder initiating stimulant treatment while not on a mood stabilizing medication had an increased risk of treatment-emergent mania (hazard ratio 6.7, 95% CI 2.0-22.4), while adults who were already receiving a mood stabilizing treatment did not (hazard ratio 0.6, 95% CI 0.4-0.9) [42].

Pregnancy — When medications are used, we prefer to use amphetamine formulations in this population. Other options include a drug holiday (for those who can reasonably tolerate it) through at least the first trimester. For patients who have a history of doing well on methylphenidate and/or cannot tolerate an amphetamine, the clinician must weigh the risk to the mother and baby if the mother is not treated.

A small increased risk of cardiac malformations has been associated with intrauterine exposure of the fetus to methylphenidate [83]. The association with cardiac malformations was not found in infants with intrauterine exposure to amphetamines. Analysis of data in a pooled sample of 1,813,894 publicly insured pregnancies in the United States and 2,560,069 infants in five Nordic countries found a higher rate of cardiac malformations in infants exposed to methylphenidate during the first trimester compared with unexposed infants (relative risk 1.28, 95% CI 1.00-1.64) [83]. Exposed and unexposed samples were balanced in rates of numerous potentially confounding variables, but the influence of unmeasured confounders could not be ruled out.

Furthermore, the proportion of reproductive-aged, privately insured women in the United States who are treated with medication for ADHD has increased over the past two decades [84]. An analysis of data on approximately 4.6 million women per year, age 15 to 44 years, found that the proportion treated with an ADHD medication increased by 344 percent over a 12-year period.

MONITORING

We monitor for positive and negative effects of medications and adverse effects at each visit [85].

Defining response — We work closely with the patient to establish what constitutes response (eg, reduction in attention deficit hyperactivity disorder [ADHD] symptoms and/or improved overall functioning) and the time course for improvement. While treatment success may be defined as remission of all ADHD symptoms, improvement in the symptoms may be clinically significant and represent observable change from baseline [85] (see 'Monitoring' above and 'Monitoring for symptomatic improvement' below and 'Monitoring for adverse effects' below). Improvement in overall functioning generally follows improvement of attention-related

symptoms. Therefore, we suggest monitoring both through the use of repeat administration of rating scales and the assessment of overall functioning with regard to work and relationships. We also obtain permission to gather collateral information from a reliable informant. Due to such issues as psychiatric comorbidity, clinicians and patients may not note immediate and/or sustained overall improvement in psychosocial functioning.

Monitoring for symptomatic improvement — We use ADHD symptom checklists to monitor symptoms throughout treatment. We find it useful to get input from other informants that are familiar with the patient as well as input from real-world collateral information such as job performance evaluation, attendance records, and grades. These may offer measures of progress tied to various performance venues that may be affected by ADHD treatment [86].

Instruments for monitoring response to treatment — We typically use the Conners' Adult ADHD Rating Scales [87] for diagnosis and determining symptom severity. We often supplement this with specific psychiatric rating scales for depression and anxiety. In addition, for patients with severe executive dysfunction, we often use the Barkley Deficits in Executive Function Scale to identify targets for treatment and monitor over time (table 2). (See "Attention deficit hyperactivity disorder in adults: Epidemiology, clinical features, assessment, and diagnosis", section on 'Assessment' and "Attention deficit hyperactivity disorder in adults: Psychotherapy", section on 'Monitoring'.)

Other reliable scales include the Reliable Change Index [88], Barkley ADHD Rating Scale IV, and the Functional Impairment Scale for Adults [89-91]. The Wender-Reimherr Adult Attention Deficit Disorder Scale [92,93] has subscales measuring temper, affective lability, and emotional overreactivity. The Weiss Functional Impairment Rating Scale [94] is useful for assessing the domain and severity of functional impairment. Other domains that can be used for monitoring treatment response include quality of life, executive functions, and processing speed [95-97].

Monitoring for adverse effects — Once the individual is on the initial target dose of medication, we see them in monthly follow-up visits until symptoms are stabilized. At each visit, we check blood pressure and pulse and address any abnormalities accordingly. We monitor ECG and work directly with a cardiologist in all individuals with baseline cardiac abnormalities. (See 'Pretreatment evaluation and contraindications' above and 'Adverse effects' above.)

SUBSEQUENT TREATMENT

For robust response — If a robust response is seen, the timing of stimulant use may still require adjustment. The negative effects of attention deficit hyperactivity disorder (ADHD) differ

across adults. We work with the individual to monitor improvement, and assist the patient in determining if medication needs adjustment for vocational, educational, or other activities. Some adults may benefit from drug holidays on weekends or holidays. However, minimal data support this approach.

Although some adults may need stimulants for a time-limited period, others may need them indefinitely. (See 'Treatment duration and continuity' below.)

For suboptimal (partial or minimal) response — For individuals with a suboptimal response to initial treatment, we review the accuracy of the diagnosis, the presence of comorbid disease and adherence to medication. We address these as indicated. (See 'Co-occurring disorders' above.)

Augmentation strategies for patients who experienced a suboptimal response to first-line medication treatment are limited. Our choice of subsequent management (eg, adjunctive psychotherapy, pharmacologic management) depends, in part, on patient preference and availability of treatment.

Adjunctive psychotherapy — For all individuals who were not started on combination treatment who are now agreeable to psychotherapy, we augment a suboptimal response to medication with cognitive-behavioral therapy (CBT) targeting executive functioning. (See 'Preference for combination medication and CBT' above and "Attention deficit hyperactivity disorder in adults: Psychotherapy".)

For noncomorbid ADHD — For adults with noncomorbid ADHD who continue to experience clinically significant symptoms despite initial treatment with amphetamines, (and who are unwilling to augment with psychotherapy, or if it is unavailable, or has been ineffective) we suggest changing medication to a methylphenidate product. No washout or tapering is necessary in switching from one stimulant preparation to another. Our transitioning dose in switching from one stimulant to another is based on whether the switch is due to lack of response or side effects:

- **Lack of response** – If the medication is being switched due to inadequate response without side effects, we suggest initiation of the new stimulant at a dose that is equivalent to or slightly lower than the dose of the current stimulant.
- **Side effects** – If the medication is being switched due to side effects or intolerance of the initial stimulant, we suggest retitration of the new stimulant starting at the lowest or a much lower equivalent dose than the current stimulant.

Equivalent initial stimulant doses, onset and duration of effect of stimulants used in adult ADHD are listed in the table (table 1).

For patients who do not experience an adequate response to (or are unable to tolerate) a therapeutic dose of either stimulant, we favor successive trials of other nonstimulant medications followed by trials of bupropion and tricyclic antidepressants (TCAs) (see 'Alternatives to stimulant medications' above). If none of these agents are sufficiently effective, we occasionally use an alpha-2 agonist such as clonidine or guanfacine, based on their efficacy in treating children with ADHD. (See 'Treatments with limited supporting data in adult ADHD' below.)

For co-occurring disorders

- **Substance use and substance use disorder (SUD)** – For adults with ADHD and a history of an SUD who cannot tolerate or do not respond to treatment with atomoxetine, we suggest treatment with bupropion. Clinical trials have found bupropion to reduce overall symptoms of ADHD compared with placebo [68]. Additionally, bupropion has been used in the treatment of nicotine and cocaine dependence, decreasing the craving often associated with these disorders [98-100]. (See 'For noncomorbid ADHD' above.)

  In cases where atomoxetine and bupropion are not effective and there is not a history of stimulant abuse we consider a long-acting amphetamine with careful monitoring for signs of misuse, diversion, or addiction. (See "Prescription drug misuse: Epidemiology, prevention, identification, and management" and "Continuing care for addiction: Components and efficacy".)

- **Depression** – For adults with ADHD and depression whose ADHD symptoms do not respond to treatment with bupropion, we suggest treatment with the combination of a long-acting stimulant for ADHD and a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI) for depression. We are careful in prescribing the combination of an SSRI and a stimulant due to the possibility of serotonin syndrome. (See 'Anxiety disorders' above and "Serotonin syndrome (serotonin toxicity)".)

  If the combination of an SSRI or an SNRI and a stimulant is ineffective (or due to adverse effects) a TCA is a reasonable alternative. Tricyclics have demonstrated efficacy in ADHD similar to their efficacy in depression [72] and similar to bupropion's treatment of ADHD, but with more side effects (table 3). (See 'For noncomorbid ADHD' above.)

- **Anxiety disorders** – For adults with ADHD and co-occurring generalized anxiety disorder or social anxiety disorder whose ADHD symptoms do not respond to treatment with a

long-acting stimulant combined with an SSRI or SNRI, we suggest treatment for both conditions with atomoxetine. Atomoxetine has been shown to have efficacy for both ADHD and anxiety, in the form of social anxiety disorder, in adults [57,101-103]. (See 'Norepinephrine reuptake inhibitors' above.)

If atomoxetine is poorly tolerated or ineffective, we typically treat with a TCA, such as nortriptyline. Clinical trials have shown TCAs to be effective in both ADHD [72] and generalized anxiety disorder [81], although with somewhat greater side effects than other ADHD medication. TCAs have not been subject to clinical trials in patients with co-occurring ADHD and generalized anxiety disorder. (See "Generalized anxiety disorder in adults: Management", section on 'Limited role of alternatives to SRIs as initial treatment'.)

For adults with ADHD co-occurring with **both** depression and an anxiety disorder, who cannot tolerate or do not respond to treatment with the combination of a stimulant and an SSRI or SNRI, we suggest treatment with a TCA for ADHD and both comorbid disorders. (See 'Anxiety disorders' above.)

Medication augmentation strategies have been tested in the treatment of ADHD in children/adolescents (eg, stimulants plus guanfacine extended-release); however, augmentation in adults with ADHD is not supported by research data nor by our clinical experience. (See "Pharmacology of drugs used to treat attention deficit hyperactivity disorder in children and adolescents".)

Treatments with limited supporting data in adult ADHD

- **Alpha-2 adrenergic agonists** – Little is known about the efficacy, safety, and tolerability of alpha-2-adrenergic agonists clonidine and guanfacine in adults with ADHD. Small clinical trials have not shown these medications to reduce ADHD symptoms in adults compared with placebo [104,105]. The medications have been found to be efficacious in trials with children and adolescents with ADHD, in particular for impulsivity and hyperactivity, for whom they are generally used third-line, or for certain clinical subgroups. (See "Pharmacology of drugs used to treat attention deficit hyperactivity disorder in children and adolescents", section on 'Alpha-2-adrenergic agonists'.)

- **Venlafaxine** – Venlafaxine, a serotonin-norepinephrine reuptake inhibitor antidepressant, may be mildly efficacious in reducing ADHD symptoms. A clinical trial of venlafaxine in 44 adults with ADHD did not find a statistically significant reduction in ADHD symptoms compared with placebo [106]. A greater proportion of patients receiving venlafaxine experienced a 25 percent or greater reduction in ADHD symptoms compared with patients on placebo (75 versus 20 percent).

- **SSRI** – While SSRI are often used along with stimulant medications in the treatment of comorbid ADHD with depression, there are few clinical trials of SSRI antidepressants in adults with ADHD. A randomized trial of 98 adults with ADHD and a lifetime diagnosis of an depression or anxiety disorder found no difference in the intent to treat analysis of change in ADHD symptoms among groups treated with either 40 mg/day of paroxetine, 20 mg twice daily of dextroamphetamine, or placebo [107].

- **Monoamine oxidase inhibitor antidepressants (MAOIs)** – Clinical trials of MAOIs have shown mixed results in adult ADHD. Patients with ADHD, a disorder characterized by impulsivity and inattention, may be poor candidates for treatment with these medications, which require dietary and other restrictions to avoid serious adverse events. (See "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

- **Neurostimulation** – Transcranial direct current stimulation (tDCS), a noninvasive brain stimulation technique, may improve symptoms of inattention in adults with ADHD who are not taking stimulant or nonstimulant medications. In a randomized trial, 64 individuals with ADHD were treated with 28 sessions (over four weeks) of daily home-based tDCS versus sham tDCS to the right dorsolateral prefrontal cortex [108]. At the end of treatment, individuals receiving tDCS scored lower on measures of inattention (Adult ADHD Self-report scale [36 points, nine questions]) than those receiving sham tDCS (18.9 versus 23.6, respectively). However, effects on hyperactivity-impulsivity, depression, or anxiety symptoms were similar between groups. Further studies evaluating the effects of tDCS for adults with ADHD, including intensity, duration and number of sessions are needed.

- **Other agents and complementary or alternative treatments** – Trials of L-deprenyl [109], pargyline [110], modafinil [111], and cholinesterase inhibitors [112] have provided little evidence of efficacy of these agents in treating ADHD in adults.

    - **Cannabinoids and cannabinoid products** – Despite common belief that cannabinoids and cannabinoid products, including tetrahydrocannabinol (marijuana) have benefits for ADHD, few studies support the drug's effectiveness for ADHD in adults. Additionally, cannabis use appears to acutely impair cognitive functions such as attention, concentration, and episodic memory [113-115]. These effects are time limited and dependent on dose, route of administration, and degree of tolerance.

      In a trial 30 adults with ADHD were randomly assigned to treatment with pharmaceutical delta-9-tetrahydrocannabinol (THC):cannabidiol (CBD) versus placebo

[52]. Results showed similar effects on primary outcome of ADHD symptoms. At this time, marijuana or other cannabinoids cannot be safely recommended for the treatment of ADHD.

- **Micronutrients** – There are few clinical trials of complementary/alternative treatments for adult ADHD. In a randomized trial of 80 adults with ADHD, micronutrients (vitamins and minerals) were compared with placebo over eight weeks [116]. Subjects receiving micronutrients were rated by themselves and observers as improved at the end of the trial. Clinician ratings found mixed results, with some ADHD scales showing improvement and others not.

TREATMENT DURATION AND CONTINUITY

The negative effects of attention deficit hyperactivity disorder (ADHD) differ across adults. Some adults may need stimulants for a time-limited period, while others may need them indefinitely. In some cases, drug holidays on weekends or holidays are useful. After providing information about the potential benefits and adverse events associated with stimulant treatment of ADHD, we advocate shared decision-making with the clinician reviewing potential therapeutic options and possibly making a recommendation. As with other clinical decisions described in this report and unless contraindicated, the adult patient has the final word in deciding which of the therapeutic options to follow.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Attention deficit hyperactivity disorder".)

SUMMARY AND RECOMMENDATIONS

- **Initial treatment for most** – For most adults with attention deficit hyperactivity disorder (ADHD), we suggest initial treatment with a combination of medication management and cognitive-behavioral therapy (CBT) targeting executive dysfunction, rather than either treatment alone (algorithm 2) (**Grade 2C**). (See 'Initial Treatment' above.)

  - **Amphetamines as initial pharmacologic treatment** – For most adults with ADHD, we suggest initial pharmacologic management with an amphetamine rather than

methylphenidate (**Grade 2C**) (table 1). (See 'Choosing a stimulant' above.)

- **Pharmacologic treatment for specific populations** – Alternative medication and treatments may be the preferred initial therapy in some patients. (See 'Alternatives to stimulant medications' above and 'Initial treatment for specific populations' above.)
  - **For co-occurring substance use or substance use disorder (SUD)**
    - In individuals with an active SUD and comorbid ADHD, we stabilize the SUD prior to treating ADHD. (See 'Active substance use disorder' above.)
    - For individuals with a history of SUD or substance misuse (eg, benzodiazepines, alcohol, opioids, stimulants), we suggest first-line choice of treatment with the nonstimulant atomoxetine (algorithm 1) (**Grade 2C**). (See 'History of substance use disorder' above.)
  - **Co-occurring depression** – For adults with ADHD and co-occurring depression, we treat with bupropion. Bupropion has evidence of efficacy in both patients with ADHD and in patients with depression (**Grade 2C**). (See 'Depression' above.)
  - **Co-occurring anxiety** – For adults with ADHD and co-occurring generalized or social anxiety disorders, we treat the disorders at the same time with a combination of a stimulant and a selective serotonin reuptake inhibitor (SSRI). We typically start the SSRI first and the stimulant when the anxiety is lessened. (See 'Anxiety disorders' above.)
  - **Pregnancy** – For pregnant patients, we avoid methylphenidate when possible due to the risks to the fetus. We consider a drug holiday in pregnancy (for those who can reasonably tolerate it) at least through the first trimester. When medications are used, we prefer to use amphetamines. (See 'Pregnancy' above.)
- **Subsequent treatment**
  - **For robust response** – If a robust response is seen, the timing of stimulant use may still require adjustment particularly for vocational activities and educational activities. (See 'For robust response' above.)
  - **Partial response** – For individuals with a suboptimal response to initial treatment we review the accuracy of the diagnosis, the presence of comorbid disease and adherence to medication. We address these as indicated. (See 'For suboptimal (partial or minimal) response' above.)

- **Adjunctive psychotherapy** – For individuals initially treated with medication alone who have a suboptimal response, we suggest augmentation with CBT targeting executive functioning (**Grade 2C**). Combination therapy with CBT and pharmacotherapy appears to be the most efficacious treatment for adults with ADHD. (See 'Adjunctive psychotherapy' above.)

- **Medication adjustment** – For adults with noncomorbid ADHD who continue to experience clinically significant symptoms despite treatment with amphetamines (either in conjunction with cognitive processing therapy or when CBT is not available), we suggest changing treatment to a methylphenidate product (**Grade 2C**). (See 'For noncomorbid ADHD' above.)

  For individuals with poor response or lack of tolerance to two prior stimulants, we favor successive trials of atomoxetine, bupropion, or a tricyclic antidepressant such as nortriptyline in addition to augmentation with CBT. Only limited data support these medications for treatment of ADHD in adults.

Topic 118534 Version 22.0

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