Atypical antidepressants: Pharmacology, administration, and side effects

AUTHORS: Michael Hirsch, MD, Robert J Birnbaum, MD, PhD
SECTION EDITOR: Peter P Roy-Byrne, MD
DEPUTY EDITOR: David Solomon, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Oct 2023.**
This topic last updated: **Mar 21, 2023.**

INTRODUCTION

Advances in understanding brain neurophysiology have led to the development of atypical antidepressants, including [1]:

- Agomelatine (not available in the United States)
- Bupropion
- Mirtazapine

The atypical antidepressants are distinct from other classes of antidepressants that include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, serotonin modulators, tricyclics, and monoamine oxidase inhibitors. Atypical antidepressants are frequently used in patients with major depression who have inadequate responses or intolerable side effects during first-line treatment with SSRIs [2]. However, atypical antidepressants are often first-line treatment if the drug has a desirable characteristic (eg, sexual side effects and weight gain occur less often with bupropion than SSRIs).

The pharmacology, administration, and side effects of atypical antidepressants are reviewed here. Choosing a regimen for the initial treatment of depression and treatment of resistant depression is discussed separately, as are other antidepressant drug classes:

- (See "Unipolar major depression in adults: Choosing initial treatment".)

- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)
- (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)
- (See "Serotonin modulators: Pharmacology, administration, and side effects".)
- (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)
- (See "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

GENERAL PRINCIPLES

Drug-drug interactions — Bupropion may inhibit hepatic cytochrome P4502D6 enzymes that metabolize other medications and thereby cause drug-drug interactions [3]. By contrast, agomelatine and mirtazapine do not moderately or potently inhibit P450 enzymes, and may thus be of benefit to depressed patients who are receiving other medications for general medical conditions. Specific interactions of atypical antidepressants with other medications may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Guidelines to review with patients — Prior to prescribing atypical antidepressants, clinicians should discuss:

- Drug interactions
- Side effects
- Time to response
- Stopping the medication

Common and serious side effects and the need to take the medication as prescribed rather than on an as needed basis should be reviewed. Patients should also be informed that although some response may occur within the first two weeks of treatment, it may take many weeks (eg, 8 to 14) for a full response (severity of illness and comorbid disease may affect how quickly depressed patients respond to treatment) [4].

Medical tests and plasma levels — No specific medical tests are required before starting atypical antidepressants. However, clinicians who prescribe agomelatine and wish to comply with recommendations from the European Medicines Agency should check liver function tests at baseline prior to initiating treatment, and then after 6, 12, and 24 weeks of treatment.

Atypical antidepressant serum concentrations are not routinely monitored because they have not been shown to correlate with clinical response [5]. However, levels can assess adherence and whether unresponsive patients are rapid metabolizers. Levels can also establish that it is safe to begin another serotonergic drug (eg, a monoamine oxidase inhibitor) after discontinuing an antidepressant that has serotonergic properties (eg, bupropion), in order to avoid the serotonin syndrome (table 1). (See "Serotonin syndrome (serotonin toxicity)".)

Dosing — We suggest starting with the lowest minimal effective dose in order to avoid side effects and slowly increasing the dose as needed. Starting doses and target dose ranges of each atypical antidepressant are listed in the table (table 2). Depressed patients with comorbid anxiety disorders may tolerate the medication better by starting with half of the suggested dose. Doses are adjusted according to patient response, tolerability, and clinical urgency.

Finding the effective dose of an antidepressant involves trial and error. After starting the drug and titrating up to the minimum effective dose, response should be monitored over the next two to four weeks. For patients who tolerate the antidepressant but do not respond, we continue titrating up the dose slowly (to avoid side effects) every two to four weeks. For unresponsive patients who do not tolerate the drug, we suggest switching to a different antidepressant. (See "Switching antidepressant medications in adults" and "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Next step treatment'.)

Patients who recover from an episode of major depression should generally receive maintenance treatment with the full dose that successfully resolved the episode, rather than a lower dose. (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Dose'.)

Pregnancy — Treatment of pregnant women with antidepressants is discussed separately. (See "Severe antenatal unipolar major depression: Choosing treatment".)

Suicide — The potential effect of atypical antidepressants on suicidal ideation and behavior in adults is discussed separately. (See "Effect of antidepressants on suicide risk in adults".)

AGOMELATINE

Agomelatine is used to treat major depression, but is contraindicated in patients with liver disease and patients taking medications that are potent inhibitors of the liver cytochrome P450 enzyme 1A2. The drug is not available in the United States.

Pharmacology — Agomelatine is a bicyclic naphthalenic compound whose structure resembles that of melatonin [6,7]. Agomelatine acts as an agonist at melatonin receptors (MT1 and MT2) that are thought to provide beneficial effects upon sleep disturbances by helping to restore normal circadian rhythms [8]; patients with insomnia may thus prefer agomelatine [8,9]. The drug also antagonizes the serotonergic 5-HT2C receptor, which in turn enhances release of dopamine and norepinephrine. Agomelatine has no effect upon extracellular serotonin levels or monoamine uptake, and has no affinity for adrenergic, cholinergic, dopaminergic, and histaminergic receptors [6,7,10].

The pharmacokinetic parameters of agomelatine are displayed in the table (table 3). Agomelatine is metabolized in the liver primarily by the P450 enzyme CYP1A2, and is contraindicated in patients taking medications that potently inhibit the enzyme. As an example, co-administration with fluvoxamine has been demonstrated in vivo to raise agomelatine serum concentrations 60-fold [10]. Specific interactions of agomelatine with other medications may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

The serum concentration of agomelatine may be lowered in heavy smokers, via induction of CYP1A2.

Administration, dose, and discontinuation — The usual starting dose of agomelatine for major depression is 25 mg per day at bedtime (table 2) [5]. For patients who do not respond after two to four weeks, the dose is increased to 50 mg per day.

Abrupt discontinuation of agomelatine 25 mg per day does not cause withdrawal symptoms. In a randomized trial, 88 patients with major depression who remitted during 12 weeks of treatment with agomelatine 25 mg per day were assigned to continue treatment or to placebo for two weeks; the number of discontinuation symptoms was comparable for the two groups [11]. However, for patients receiving agomelatine 50 mg per day, we suggest tapering the drug over one week, which is consistent with the preferred method of discontinuing any psychotropic medication.

Side effects — Agomelatine may be hepatotoxic and is avoided in patients with active liver disease [12]. A pooled analysis of randomized trials found that elevation of serum transaminases >3 times the upper limit of normal was greater for agomelatine 50 mg per day than placebo (1.3 versus 0.3 percent of patients) [13]. Thus, the European Medicines Agency

requires liver function tests at baseline; after 6, 12, and 24 weeks of treatment; and when clinically indicated thereafter [13].

Other side effects are generally infrequent (table 4). In a pooled analysis of 13 randomized trials that compared agomelatine with placebo in 3034 patients with unipolar major depression, adverse effects that occurred more frequently with agomelatine included [5,13]:

- Dizziness – 6 percent of patients who received agomelatine
- Insomnia – 3 percent
- Paresthesia – 1 percent
- Blurred vision – 1 percent
- Sinusitis – 1 percent

Based upon randomized trials, agomelatine does not cause weight gain, gastrointestinal distress, cardiovascular toxicity, or sexual impairment [14].

In addition, the tolerability of agomelatine may be superior to that of selective serotonin reuptake inhibitors (SSRIs) or venlafaxine. A meta-analysis of nine randomized trials (3377 patients with major depression) compared agomelatine with SSRIs (escitalopram, fluoxetine, paroxetine, or sertraline) and found that discontinuation of treatment due to side effects occurred less often with agomelatine (risk ratio 0.7, 95% CI 0.5-0.9) [15]. In addition, drop out due to side effects was less with agomelatine than venlafaxine (two trials, 608 patients; risk ratio 0.3, 95% CI 0.2-0.6).

Overdose — Case reports of patients who overdosed on agomelatine describe epigastralgia, somnolence, fatigue, agitation, anxiety, tension, dizziness, cyanosis, or malaise [10]. One patient ingested 2450 mg and recovered spontaneously.

BUPROPION

Bupropion is used to treat major depression, seasonal affective disorder, attention deficit hyperactivity disorder, tobacco dependence, hypoactive sexual disorder, and obesity [16,17].

Contraindications include bulimia nervosa, anorexia nervosa, use of monoamine oxidase inhibitors in the past two weeks, seizure disorders, and abrupt withdrawal from alcohol, benzodiazepines, or other sedatives. In addition, bupropion should be used cautiously in patients receiving other drugs that can lower seizure threshold. Additional information about drug-drug interactions are discussed elsewhere in this topic. (See 'Drug-drug interactions' above.)

Pharmacology — Bupropion is a monocyclic aminoketone that is structurally related to amphetamine [18]. Some authorities classify the drug as a dopamine norepinephrine reuptake inhibitor, because it inhibits presynaptic reuptake of dopamine and norepinephrine (with a greater effect upon dopamine) [1,19]. The drug has little effect upon other neurotransmitters, and little to no affinity for postsynaptic receptors [18,20].

The pharmacokinetic parameters of bupropion are displayed in the table (table 3). Bupropion is metabolized in the liver by the cytochrome P450 enzyme 2B6; medications that inhibit this enzyme may increase the plasma concentration of bupropion and thus raise the risk of seizure. Specific interactions of bupropion with other medications may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Administration, dose, and discontinuation — Bupropion is available as three formulations that are bioequivalent and dosed as follows for major depression (table 2) [16,18,21-23]:

- **Immediate release** – Typically started at 100 mg twice daily; for patients who do not respond after two to four weeks, the dose is increased to 100 mg three times daily. For patients who remain unresponsive after two to four weeks, the dose is increased to 150 mg three times daily. The maximum single dose is 150 mg.

- **Sustained release** – Typically started at 150 mg once daily; for unresponsive patients who do not respond after two to four weeks, the dose is increased to 150 mg twice daily. For patients who remain unresponsive after two to four weeks, the dose is increased to 200 mg twice daily. The maximum single dose is 200 mg.

- **Extended release** – Typically started at 150 mg once daily; for patients who do not respond after two to four weeks, the dose is increased to 300 mg once daily. For patients who remain unresponsive after two to four weeks, the dose is increased to 450 mg daily. The maximum single dose in the United States is 450 mg and in Europe is 300 mg per day. The extended release formulation is intended to be swallowed whole and not divided, crushed, or chewed.

In clinically urgent situations such as inpatient treatment, the dose of each formulation can be titrated up after three days. For patients with renal or hepatic impairment, we generally decrease the dose by at least 50 percent [22].

There appear to be no significant withdrawal symptoms upon discontinuation of bupropion. Nevertheless, we taper the drug over one to two weeks before stopping it, which is consistent with the preferred method of discontinuing any psychotropic medication.

Side effects — Seizures may occur with bupropion and the incidence appears to be correlated with dose. The rate with the [16,23]:

- Immediate release formulation at doses of 300 to 450 mg per day is 0.4 percent; however, the incidence increases approximately 10 fold at higher doses of up to 600 mg per day.
- Sustained release formulation (which allows for lower peak plasma concentrations) at doses of 100 to 300 mg per day is 0.1 percent, and at 400 mg per day is 0.4 percent.
- Extended release formulation at doses ≤450 mg per day is 0.1 percent.

By comparison, the estimated rate of seizures in patients treated with selective serotonin reuptake inhibitors (SSRIs) is 0.1 percent, tricyclics 0.4 to 2 percent, and in the general population is 0.07 to 0.09 percent [24]. Seizures appear to be especially problematic in patients with bulimia nervosa or anorexia nervosa, and bupropion is contraindicated in these patients; a randomized trial in which the drug was given to 55 nondepressed patients with bulimia nervosa found that generalized tonic-clonic seizures occurred in 4 (7 percent) [25].

Bupropion can cause several other side effects (table 4). A pooled analysis of four randomized trials compared bupropion extended release (300 to 450 mg per day) with placebo in 991 patients with major depression for 8 or 12 weeks; adverse effects that occurred at least twice as often with bupropion than placebo included [26]:

- Dry mouth – 21 percent of patients who received bupropion
- Nausea – 13 percent
- Insomnia – 12 percent
- Dizziness – 10 percent
- Anxiety – 6 percent
- Dyspepsia – 6 percent
- Sinusitis – 5 percent
- Tremor – 5 percent

The most common side effects (eg, dry mouth, nausea, and insomnia) of bupropion extended release are similar to those of the other two formulations [17,27]. However, the relative tolerability of the different formulations has not been directly compared.

Weight loss can occur with bupropion. A meta-analysis found that patients lost approximately 1 kg [28]. As an example, an eight week randomized trial in 274 patients with unipolar major depression found that bupropion extended release (300 or 450 mg per day) led to a mean weight loss of 1.1 kg, whereas placebo led to a mean weight increase of 0.2 kg [29].

Bupropion may be preferred by patients who want to minimize the risk of antidepressant-induced sexual dysfunction. In addition, depressed patients with sexual dysfunction induced by SSRIs may find that adjunctive bupropion (300 mg per day) can improve desire and frequency of sexual activity. The use of bupropion monotherapy to avoid sexual side effects, and augmentation of SSRIs with bupropion to relieve sexual side effects, are discussed separately. (See "Sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs): Management".)

Patients may notice bupropion is mildly stimulating, which may be interpreted as anxiety and can lead to insomnia if given shortly before bedtime. This stimulant-like effect may be beneficial in depressed patients with fatigue, hypersomnia, or poor concentration [23]. A retrospective study of administrative claims data suggests that the drug's stimulating effects may possibly lead to diversion and misuse [30]; however, the low quality of this evidence leads us to suggest that clinicians should generally not change their practice with regard to using bupropion.

Although some studies indicate that bupropion has minimal effects upon blood pressure [29,31], other studies suggest that it may raise blood pressure, especially if it is used in conjunction with the transdermal nicotine patch [32].

For many drugs, side effects are associated with peak plasma concentrations [16]. The once daily extended release and twice daily sustained release formulations of bupropion reduce the number of exposures to peak concentrations, compared with the thrice daily immediate release formulation. Discontinuation of treatment due to side effects in randomized trials was greater for bupropion sustained release than placebo, and comparable for extended release and placebo:

- In a pooled analysis of three trials that compared bupropion sustained release (100 to 400 mg per day) with placebo for eight weeks in 1420 patients with major depression, discontinuation of treatment due to side effects occurred in more patients who received bupropion than placebo (7 versus 4 percent) [27].

- A pooled analysis of five randomized trials that compared bupropion extended release (150 to 450 mg per day) with placebo for eight weeks in 1597 patients with major depression found that discontinuation of treatment due to side effects was comparable with bupropion and placebo (5 versus 4 percent) [23].

Overdose — Overdose of bupropion can cause seizures, hypertension, tachycardia, arrhythmias, and death. (See "Acute poisoning from atypical (non-SSRI) antidepressants, including serotonin modulators and serotonin-norepinephrine reuptake inhibitors (SNRIs)", section on 'Bupropion'.)

MIRTAZAPINE

Mirtazapine is used to treat major depression, generalized anxiety disorder, and tension type headaches.

Pharmacology — Mirtazapine is a piperazinoazepine compound that has a tetracyclic structure [33,34]. However, the drug is not related to the tetracyclic antidepressant maprotiline, which is classified with the tricyclic antidepressants because it blocks reuptake of serotonin and norepinephrine. By contrast, mirtazapine is not a reuptake inhibitor, and some authorities classify mirtazapine as a noradrenergic and specific serotonergic antidepressant because it antagonizes presynaptic alpha-2 adrenergic receptors and postsynaptic serotonin 5-HT2 and serotonin 5-HT3 receptors. Blockade of the adrenergic receptors increases release of norepinephrine and serotonin. Blockade of the serotonergic receptors increases neurotransmission mediated by serotonin 5-HT1 receptors. In addition, mirtazapine has a high affinity for histamine H1 receptors (which probably accounts for the drug's sedative properties). Mirtazapine has low affinity for cholinergic, alpha-1 adrenergic, and dopaminergic receptors.

The pharmacokinetic parameters of mirtazapine are displayed in the table (table 3). Drug-drug interactions with mirtazapine are generally not a problem because the drug is not a potent or moderate inhibitor of hepatic cytochrome P450 enzymes [3].

Administration, dose, and discontinuation — The usual starting dose of mirtazapine for major depression is 15 mg at bedtime (table 2). For patients who do not respond after two to four weeks, the dose is increased to 30 mg at bedtime. For patients who remain depressed after two to four weeks, the dose is increased to 45 mg at bedtime; some patients may require another increase to 60 mg [35]. The dose can be titrated up more quickly in clinically urgent situations (eg, inpatient treatment), by 15 mg increments every week. For patients with severe renal (creatinine clearance <40 mL/minute) or hepatic impairment, we generally limit the dose to 30 mg per day due to decreased clearance of the drug [34].

The relationship between the dose and side effects of mirtazapine is unusual, in that sedation appears more pronounced at doses of 15 mg daily than at doses ≥30 mg daily; this may be due to increased noradrenergic neurotransmission as the dose is increased [34]. Dosing may be initiated at 30 mg or more in order to reduce sedation. It is not clear whether side effects other than sedation are reduced at higher doses (30 or 45 mg per day).

The drug is available as an oral, rapidly dissolving tablet, which can be useful for patients with swallowing difficulties and gastrointestinal disorders [33].

Abrupt discontinuation of mirtazapine can cause discontinuation symptoms. Information about preventing the discontinuation syndrome is discussed separately. (See "Discontinuing antidepressant medications in adults", section on 'Atypical antidepressants'.)

Side effects — Mirtazapine can cause several side effects (table 4). A pooled analysis of randomized trials that compared mirtazapine with placebo for six weeks in 814 patients with major depression found that discontinuation of treatment due to side effects for mirtazapine was 16 percent and for placebo 7 percent [33,36].

The frequency of specific side effects was examined in a pooled analysis of randomized trials that included 1726 patients with major depression; adverse effects that occurred more frequently with mirtazapine than placebo included [37]:

- Dry mouth – 25 percent of patients who received mirtazapine
- Drowsiness – 23 percent
- Sedation – 19 percent
- Appetite increased – 11 percent
- Weight increased – 10 percent

Sexual dysfunction with mirtazapine and placebo appear to be comparable, based upon a meta-analysis [38]. In addition, changes in blood pressure and pulse are comparable for mirtazapine and placebo, based upon a pooled analysis of randomized patients with major depression [37].

Mirtazapine may possibly cause agranulocytosis and neutropenia in rare instances [33,37]. However, we do not routinely monitor white blood cell counts.

Overdose — Overdose of mirtazapine is often benign. (See "Acute poisoning from atypical (non-SSRI) antidepressants, including serotonin modulators and serotonin-norepinephrine reuptake inhibitors (SNRIs)", section on 'Mirtazapine'.)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading

level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Coping with high drug prices (The Basics)")
- Beyond the Basics topics (see "Patient education: Depression treatment options for adults (Beyond the Basics)" and "Patient education: Depression in adults (Beyond the Basics)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)")

The National Institute of Mental Health also has educational material on the use of antidepressants, including SSRIs, entitled, "What medications are used to treat depression?" that is available online at the website. Material explaining the symptoms, causes, and treatment for depression is also available in a booklet entitled "Depression" that is available online at the website. Both publications can also be obtained through a toll-free number, 866-615-6464. The web site also provides references, summaries of study results in language intended for the lay public, and information about clinical trials currently recruiting patients.

The Depression and Bipolar Support Alliance (available at the website or 800-826-3632) is a national organization whose mission is to educate members about depression and how to cope with it. Other functions include increasing public awareness of the illness and advocating for more research and services. The organization is administered and maintained by patients and family members, and has local chapters.

The National Alliance on Mental Illness (available at the website or 800-950-6264) is a similarly structured organization devoted to providing education, support, and advocacy for patients with any mental illness. Depression is one of their priorities.

SUMMARY

- **Specific drugs and their indications** – Atypical antidepressants include agomelatine, bupropion, and mirtazapine. These drugs can be used for the initial treatment of major depression, as well as patients with treatment-resistant depression or other disorders. (See 'Introduction' above and "Unipolar major depression in adults: Choosing initial

treatment" and "Unipolar depression in adults: Choosing treatment for resistant depression".)

- **Drug-drug interactions** – Bupropion may inhibit hepatic cytochrome CYP2D6 enzymes that metabolize other medications and thereby cause drug-drug interactions. By contrast, agomelatine and mirtazapine do not moderately or potently inhibit P450 enzymes. (See 'Drug-drug interactions' above.)

- **Guidelines to review with patients** – Prior to prescribing atypical antidepressants, clinicians should discuss drug interactions, side effects (table 4), time to response, and stopping the medication. No specific medical tests are required before starting atypical antidepressants and drug plasma levels are not routinely performed. (See 'Guidelines to review with patients' above.)

- **Dosing** – We suggest starting with a low dose to avoid side effects, and increasing the dose slowly. Starting doses and target dose ranges of each atypical antidepressant are listed in the table (table 2). (See 'Dosing' above.)

- **Agomelatine** – Agomelatine is contraindicated in patients with liver disease and patients taking medications that are potent inhibitors of the liver cytochrome P450 enzyme 1A2. Adverse effects include dizziness. The drug is not available in the United States. (See 'Agomelatine' above.)

- **Bupropion** – Adverse effects of bupropion include seizures, dry mouth, nausea, insomnia, dizziness, anxiety, dyspepsia, sinusitis, and tremor. (See 'Bupropion' above.)

- **Mirtazapine** – Adverse effects of mirtazapine include dry mouth, drowsiness, sedation, appetite increase, and weight increase. (See 'Mirtazapine' above.)

Topic 85816 Version 20.0

→