Unipolar depression in adults: Treatment with second-generation antipsychotics

AUTHOR: Craig Nelson, MD
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: **Jan 19, 2023.**

INTRODUCTION

Second-generation antipsychotics are often indicated for unipolar major depression, as well as other psychiatric disorders such as schizophrenia and bipolar disorder. For major depression, atypical antipsychotics are used adjunctively for nonpsychotic patients who respond insufficiently to antidepressant monotherapy [1,2]. Second-generation antipsychotics in combination with an antidepressant are also effective for psychotic depression [3], and the atypical antipsychotic quetiapine is effective as monotherapy for nonpsychotic depression [4]. The efficacy of atypical antipsychotics for major depression is hypothesized to be the result of their serotonergic, noradrenergic, and dopaminergic effects [5-11].

First-generation antipsychotics have also been used to treat depression, initially as monotherapy and subsequently as adjunctive treatment with an antidepressant [12,13]. Randomized trials found that for nonpsychotic depression, first-generation antipsychotic monotherapy was superior to placebo and either comparable or superior to an antidepressant. However, the use of first-generation antipsychotics for depression has declined because of the risk of tardive dyskinesia, which is greater for first-generation than second-generation antipsychotics [14].

This topic reviews the use of second-generation antipsychotics for treating unipolar major depression. The initial treatment of depression, treatment of resistant depression, clinical

features and diagnosis of depression, and the pharmacology of second-generation antipsychotics are discussed separately.

- (See "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- (See "Unipolar depression in adults: Assessment and diagnosis".)
- (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

DEFINITION OF MAJOR DEPRESSION

An episode of major depressive disorder (unipolar major depression) is defined in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as a period lasting at least two weeks, with five or more of the following symptoms: depressed mood, loss of interest or pleasure in most activities, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, decreased energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide (table 1) [15]. Additional information about the clinical features and diagnosis of unipolar major depression is discussed separately. (See "Unipolar depression in adults: Clinical features" and "Unipolar depression in adults: Assessment and diagnosis".)

INDICATIONS

In unipolar major depression, second-generation antipsychotics are indicated for patients with:

- Nonpsychotic depression that does not respond sufficiently to antidepressant monotherapy – the antipsychotic is generally added to the same antidepressant [2]. (See "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Patients who prioritize efficacy'.)

- Psychotic depression – the antipsychotic is started concurrently with an antidepressant [16-18]. (See "Unipolar major depression with psychotic features: Acute treatment".)

In addition, the second-generation antipsychotic quetiapine may be efficacious as monotherapy for unipolar, nonpsychotic major depression, and thus an option when switching from an ineffective treatment regimen [19-21].

ADJUNCTIVE TREATMENT FOR NONPSYCHOTIC DEPRESSION

Adjunctive medications are commonly used to treat unipolar nonpsychotic depression, because many patients respond insufficiently to antidepressant monotherapy [1]. As an example, an open-label study of citalopram in 3671 patients with major depression found that remission occurred in only 37 percent [22].

Among available adjunctive medications, many authorities and clinicians choose a second-generation antipsychotic. In a study of outpatient visits for antidepressant-treated, nonpsychotic unipolar depression (n >2500), a second-generation antipsychotic was prescribed during 11 percent of the visits (20 percent of visits with psychiatrists and 5 percent of visits to other physicians) [23]. The most commonly prescribed antipsychotics were quetiapine and aripiprazole. Other choices for augmentation include lithium [24] and triiodothyronine (T_3) [25]. Additional information about augmenting an antidepressant in treatment resistant depression is discussed separately. (See "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Initial approach'.)

Efficacy — The efficacy of augmenting an antidepressant with a second-generation antipsychotic is established for acute treatment of major depression but not maintenance treatment [2,26-28].

Acute phase — The benefit of adjunctive aripiprazole, brexpiprazole, cariprazine, olanzapine, quetiapine, risperidone, or ziprasidone for acute treatment of depression has been demonstrated in randomized trials:

- A 2009 meta-analysis of 16 randomized trials compared the efficacy of add-on aripiprazole, olanzapine, quetiapine, or risperidone with placebo in 3480 patients with major depressive disorder who failed monotherapy with an antidepressant [2]. The study drug was added to the original, ongoing antidepressant in 14 of the trials; in 2 trials, the study drug and a new antidepressant were started concurrently. The trials generally lasted either six or eight weeks. Key findings included the following:
  - More patients remitted with an antipsychotic than placebo (31 versus 17 percent).
  - Discontinuation of treatment due to adverse effects was greater with an antipsychotic than placebo (9 versus 2 percent of patients). (See 'Medication doses and side effects' below.)

- Adjunctive aripiprazole, olanzapine, quetiapine, and risperidone were each superior to placebo, and no antipsychotic was superior to another.

A subsequent network meta-analysis replicated most of these findings [29]. In addition, a subsequent randomized trial found that add-on aripiprazole was beneficial for managing late-life, treatment resistant depression. (See "Diagnosis and management of late-life unipolar depression", section on 'Aripiprazole'.)

- A subsequent eight-week randomized trial compared add-on ziprasidone with placebo in patients (n = 139) with major depression who did not respond to open-label treatment with escitalopram [30]. Response (reduction of baseline symptoms ≥50 percent) was greater with ziprasidone than placebo (35 versus 21 percent of patients). However, discontinuation of treatment due to adverse effects was greater with ziprasidone than placebo (14 versus 0 percent).

- Another subsequent trial, lasting six weeks, compared adjunctive brexpiprazole with placebo in patients with major depression who did not respond to open-label treatment with antidepressant monotherapy (n = 353) [31]. Response occurred in more patients who received add-on brexpiprazole than placebo (23 versus 16 percent). However, remission with brexpiprazole occurred in only 15 percent. Discontinuation of treatment due to adverse effects with active drug or placebo occurred in 3 and 0 percent. The same group of investigators conducted a second trial using similar methods, and the results were comparable [32].

- A subsequent eight-week trial enrolled patients with unipolar major depression who, by history, had an inadequate response to at least six weeks of their current antidepressant; the patients were randomly assigned to add-on cariprazine 2 to 4.5 mg/day (n = 271) or placebo (n = 264) [33]. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received cariprazine than placebo (49 versus 38 percent). However, discontinuation of treatment due to adverse events was greater with cariprazine than placebo (13 versus 3 percent).

- Another study enrolled patients with late life depression and prospectively treated them with open-label venlafaxine; patients who did not remit (n = 181) were randomly assigned to add-on aripiprazole or placebo for 12 weeks [34]. Remission occurred in more patients who received aripiprazole than placebo (44 versus 29 percent). Discontinuation of treatment due to adverse events was only 3 percent in each group. Aripiprazole is the only adjunctive agent, of any type, shown to be effective in older adults in a randomized,

placebo-controlled study. (See "Diagnosis and management of late-life unipolar depression", section on 'Adjunctive medications'.)

No head-to-head randomized trials have been conducted to determine whether there are differences in efficacy among adjunctive aripiprazole, brexpiprazole, cariprazine, olanzapine, quetiapine, risperidone, or ziprasidone. However, secondary clinical effects may differentially affect the utility of adjunctive antipsychotics for treating major depression. As an example, quetiapine is sedating and useful for insomnia [35], whereas olanzapine causes the most weight gain, which may help patients with anorexia and excessive weight loss. By contrast, ziprasidone does not lead to weight gain. Additional secondary (side) effects are discussed separately. (See 'Medication doses and side effects' below.)

It is reasonable to use an adjunctive antipsychotic with any antidepressant. In randomized trials, the antipsychotic was usually added to a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor [2,30-33].

Improvement of depressive symptoms with adjunctive aripiprazole, olanzapine, quetiapine, or risperidone largely occurred within the first two weeks of treatment [35-39]. Thus, we suggest that clinicians wait at least this long before determining whether the drug is useful. Patients who improve less than 25 percent from baseline by week four of treatment are unlikely to respond further with longer treatment.

No randomized, placebo controlled trials have evaluated asenapine, iloperidone, lurasidone, or paliperidone as adjunctive treatment for patients with unipolar, nonpsychotic major depression that has failed antidepressant monotherapy. However, these drugs are reasonable alternatives for patients who have failed or cannot tolerate aripiprazole, brexpiprazole, cariprazine, olanzapine, or quetiapine, risperidone, or ziprasidone. Clozapine should be avoided because it can cause agranulocytosis.

Although the efficacy of adjunctive second-generation antipsychotics such as aripiprazole, brexpiprazole, olanzapine, quetiapine, and risperidone is clearly established, the magnitude of the benefit has been questioned. As an example, a review of three randomized trials that compared adjunctive quetiapine with placebo (n = 995 patients) concluded that the clinical effect was small and may not offset potential harms such as the metabolic syndrome [40]. Nevertheless, the number needed to treat for quetiapine was nine, which means that adjunctive quetiapine provided one more remission than placebo for every nine patients treated with each regimen; many clinicians view this as clinically meaningful.

Minimal response to antidepressant compared with partial response — Adjunctive second-generation antipsychotics may be effective for patients with either a minimal response

to antidepressant monotherapy or a partial response [41]. Although it is commonly thought that augmentation is more useful to increase the improvement achieved in partial responders than in minimal responders [42,43], this is not established. A pooled analysis of three randomized trials compared adjunctive aripiprazole (2 to 20 mg per day) with placebo in patients with unipolar major depression who were initially treated eight weeks with open-label antidepressant monotherapy, and had either a minimal response (improvement from baseline on the depression rating scale <25 percent) or partial response (improvement of 25 to 49 percent) [44]. The primary findings after six weeks of adjunctive treatment were as follows:

- Among 746 patients with an initial minimal response, remission occurred in significantly more patients who received adjunctive aripiprazole than placebo (24 versus 12 percent).
- Among 292 patients with an initial partial response, remission was larger for adjunctive aripiprazole than placebo (41 versus 31 percent), but the difference was not statistically significant.

In addition, adjunctive antipsychotics may benefit patients who worsen during initial treatment with antidepressant monotherapy [45].

Comparisons with other adjunctive medications — Randomized trials that compared add-on second-generation antipsychotics with other add-on medications, for major depression that had failed antidepressant monotherapy, include the following:

- One open-label, six-week, randomized trial compared adjunctive quetiapine (300 mg/day) with lithium (0.6 to 1.2 mmol/L) in patients (n = 450) with unipolar major depression who, by history, did not respond to at least one antidepressant [46]. Remission with add-on quetiapine and add-on lithium was comparable (32 and 27 percent of patients). In addition, discontinuation of treatment due to adverse events appeared to be comparable with quetiapine and lithium (10 and 8 percent).
- Another open-label, six-week, randomized trial enrolled patients with unipolar major depression who by history, did not respond to at least four weeks of selective serotonin reuptake inhibitor treatment (n = 103), and randomly assigned them to aripiprazole (mean dose 3 mg/day) or bupropion (mean dose 199 mg/day) [47]. Although most outcomes were comparable for the two groups, remission occurred in more patients who received aripiprazole than bupropion (55 versus 34 percent). Discontinuation of treatment was comparable for aripiprazole and bupropion (25 versus 23 percent of patients), no patients discontinued treatment because of adverse events, and the incidence of extrapyramidal symptoms and of akathisia was comparable for the two groups.

- A third open-label trial, lasting 12 weeks, found that remission with either add-on aripiprazole or add-on bupropion was comparable [48]. However, response (reduction of baseline symptoms ≥50 percent) was modestly greater with adjunctive aripiprazole (74 versus 66 percent), and withdrawal for lack of response with adjunctive aripiprazole was half of that for adjunctive bupropion (3 and 6 percent). This trial is discussed in greater detail separately. (See "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Efficacy of primary treatment strategies'.)

The meta-analysis of 16 randomized trials (3480 patients with major depression) of adjunctive second-generation antipsychotics represents the most rigorous body of evidence for any type of adjunctive treatment in depression [2]. By contrast, the nine randomized trials of adjunctive lithium included only 237 depressed patients, many of whom would not meet current criteria for treatment resistance, and only three trials (n = 76 patients) used lithium to augment a second-generation antidepressant [24]. Comparisons between lithium and other adjunctive agents are discussed separately. (See "Unipolar depression in adults: Treatment with lithium", section on 'Compared directly with other drugs'.)

Maintenance phase — For patients with unipolar major depression who have failed multiple treatment regimens and then responded to adjunctive second-generation antipsychotics that are well-tolerated, it is reasonable to continue the antipsychotic to prevent relapse. As an example, a 27-week randomized maintenance trial compared fluoxetine (25 or 50 mg per day) plus olanzapine (6, 12, or 18 mg per day) with fluoxetine monotherapy in patients with treatment resistant depression who initially responded to acute and continuation treatment with open-label fluoxetine plus olanzapine (n = 444) [49]. There were fewer recurrences in patients who received fluoxetine plus olanzapine than fluoxetine alone (16 versus 32 percent). However, adjunctive olanzapine caused more weight gain, and clinically significant weight gain (≥7 percent) in occurred in 56 percent of patients who received olanzapine in all three study phases (up to 47 weeks). Adverse changes in glucose, triglycerides, cholesterol, and prolactin also occurred more frequently with olanzapine plus fluoxetine.

However, another randomized trial found no benefit for maintenance treatment with adjunctive second-generation antipsychotics. In the trial, patients with unipolar major depression unresponsive to citalopram monotherapy (20 to 60 mg per day) were given open-label adjunctive risperidone (0.25 to 2 mg per day) [26]. The patients who remitted or were much improved (n = 241) were treated for six months with citalopram plus risperidone or citalopram plus placebo; relapse rates for the two groups were comparable.

Safety issues — The benefits of adjunctive second-generation antipsychotics need to be weighed against safety issues that include the metabolic syndrome, and the less common but

serious problems of tardive dyskinesia and neuroleptic malignant syndrome (NMS).

Metabolic syndrome — Weight gain, diabetes, and hyperlipidemia are elements of the metabolic syndrome that can occur with second-generation antipsychotics, although the frequency of these problems appears to vary depending upon the specific drug that is used (table 2). Rates of the metabolic syndrome during randomized trials of adjunctive atypical antipsychotics in patients with unipolar major depression have not been reported [35,50,51]. However, a meta-analysis of four observational studies with 1745 patients found that a higher rate of the metabolic syndrome was associated with use of antipsychotic medication [52].

Additional information about the metabolic side effects of antipsychotics is discussed separately in the context of schizophrenia. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Endocrinologic and metabolic side effects' and "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Metabolic dysregulation'.)

Weight gain — Weight gain was common during short-term randomized trials of adjunctive second-generation antipsychotics [35,50,51], especially with olanzapine. A pooled analysis of two adjunctive aripiprazole trials suggested that weight gain may be greater during combination treatment with an antidepressant in unipolar major depression, compared with weight gain reported in monotherapy trials in schizophrenia or bipolar disorder [53]. However, one trial found that although patients with late life depression gained more weight with adjunctive aripiprazole than placebo, change in body fat was comparable for the two groups, suggesting cardiometabolic risk was not affected [34].

Long-term treatment may cause additional weight gain. In a randomized trial (n = 386), adjunctive risperidone caused weight gain ≥7 percent of body weight from baseline to end point of study phase in 3 percent of the patients during the initial 4- to 6-week open-label phase, and in another 8 percent of patients during the 24-week double-blind phase [26]. It is worth mentioning that major depression may cause weight loss; thus, weight gain may be desirable in some patients.

Tardive dyskinesia — Although tardive dyskinesia is less common with second-generation antipsychotics than first-generation antipsychotics (table 2) [14], it is still a concern because tardive dyskinesia may be irreversible, depressed patients may be at greater risk, and tardive dyskinesia is not associated with most other augmentation options. The risk of tardive dyskinesia with second-generation antipsychotics in unipolar major depression is not well established:

- **Aripiprazole** – A 52-week, open-label study of adjunctive aripiprazole in 994 patients with unipolar major depression found four cases of possible tardive dyskinesia that all resolved within 45 days of drug discontinuation [54]. Without a control group, this rate may overestimate the rate of tardive dyskinesia due to drug.

- **Brexpiprazole** – In two 52-week, open-label studies of 2084 patients with unipolar major depression who were treated with adjunctive brexpiprazole, one case of oral-buccal dyskinesia was observed [55]. The dyskinesia resolved 22 days after stopping the drug.

- **Olanzapine**

  - A 12-week, randomized trial of olanzapine in 259 patients with unipolar psychotic depression found that tardive dyskinesia occurred in 8 percent [3]. However, it appears that this rate may have reflected prior antipsychotic use and very sensitive criteria rather than new cases of tardive dyskinesia [56].

  - No new cases of tardive dyskinesia were found in a 76-week open-label study of adjunctive olanzapine in 560 patients with unipolar major depression [57].

- **Quetiapine** – A 52-week, randomized monotherapy maintenance trial in 391 patients with unipolar major depression assigned to quetiapine did not find evidence of tardive dyskinesia [58].

- **Risperidone** – Rates of tardive dyskinesia have not been reported for adjunctive risperidone in unipolar major depression during long term treatment [26].

Additional information about the risk of tardive dyskinesia with second-generation antipsychotics is discussed separately. (See "Tardive dyskinesia: Etiology, risk factors, clinical features, and diagnosis", section on 'Causative agents'.)

Neuroleptic malignant syndrome — NMS can occur with second-generation antipsychotics [59,60]. However, rates of NMS for atypical antipsychotics are not established in part because of the large sample required to reasonably estimate the rate of a rarely occurring event. In addition, bias may exist in that an atypical agent is likely to be given to patients who require an antipsychotic and have a prior history of NMS. NMS is discussed separately. (See "Neuroleptic malignant syndrome".)

Suicidal thinking and behavior in young adults — The second-generation antipsychotics carry a class warning (product information in the United States) about a possible increased risk of suicidal ideation or suicide attempt in patients under the age of 25 years. However, this risk was not established in trials of atypical antipsychotics, and this risk may be reduced if adjunctive

treatment is begun six to eight weeks after the patient has received an antidepressant. Second-generation antipsychotics may potentially be useful for treating suicidal ideation as well as symptoms such as agitation, anxiety, and insomnia, which may aggravate suicidal thinking and behavior.

- A preplanned, pooled analysis of two randomized trials examined suicidal ideation in 936 patients (age 18 to 65 years) with major depression who did not respond sufficiently to antidepressant monotherapy and subsequently received adjunctive quetiapine (150 mg or 300 mg per day) or placebo for six weeks [35]. Treatment-emergent suicidal ideation occurred in more patients who received placebo than in those who received quetiapine (2.6 versus 0.6 and 1.0 percent; not tested statistically).

- A post hoc, pooled analysis of two randomized trials examined suicidal ideation in 702 patients (age >25 years) with major depression who did not respond sufficiently to antidepressant monotherapy and subsequently received adjunctive aripiprazole (2 to 20 mg per day) or placebo for six weeks [61]. Treatment-emergent suicidal ideation occurred in significantly more patients who received placebo than aripiprazole (relative risk 0.14, 95% CI 0.03-0.60).

However, treatment emergent suicidality with adjunctive second-generation antipsychotics in unipolar major depression has not been well studied in patients who are under 25 years of age and at greatest risk.

Medication doses and side effects — The dose of an adjunctive second-generation antipsychotic for nonpsychotic unipolar major depression is often lower than the dose used for schizophrenia or bipolar disorder [31,32,36,37,62,63]. In addition, the methods used in randomized trials of adjunctive second-generation antipsychotics for major depression may suggest the need for doses that are higher than necessary. Clinicians may thus find that doses at the lower end of the range that was used in the trials are effective in many patients; higher doses can be reserved for patients with an inadequate response to the antipsychotic or severely ill patients requiring an especially fast response.

Therapeutic serum concentrations have not been established for adjunctive second-generation antipsychotics in major depression and are not used to guide dosing. Nevertheless, serum concentrations of adjunctive antipsychotics may be affected by drug-drug interactions with an antidepressant. Conversely, the antipsychotics appear to have minimal effects on the clearance of other drugs. Specific interactions of second-generation antipsychotics with antidepressants may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Short-term use of adjunctive atypical antipsychotics for depression is usually well tolerated; however, randomized trials have found that discontinuation of treatment due to adverse effects was generally greater with antipsychotics than placebo. In a pooled analysis of 16 randomized trials involving adjunctive aripiprazole, olanzapine, quetiapine, or risperidone in 3480 patients with major depression who failed monotherapy with an antidepressant, withdrawal from the study because of side effects was higher in patients who received an antipsychotic compared with placebo (9 versus 2 percent) [2]. Treatment of approximately 17 patients with the antipsychotic caused discontinuation in one additional patient that would not have occurred with placebo (number needed to harm of 17, which is generally regarded as not clinically significant [64]). The drop-out rate due to side effects varied from 4 percent (aripiprazole) to 12 percent (quetiapine), but the differences among the four atypical antipsychotics were not statistically significant [2]. In a subsequent randomized trial (n = 139 patients), discontinuation of treatment due to side effects was greater with add-on ziprasidone than placebo (14 versus 0 percent) [30]. However, in the two brexpiprazole trials, discontinuation rates due to adverse events were low for active drug and placebo (3 and 1 percent) [31,32].

The side effect profile for each antipsychotic is different (table 2). As an example, studies of adjunctive second-generation antipsychotics for unipolar major depression suggest that the following drugs may be more likely to cause specific adverse effects [65]:

- Aripiprazole – akathisia
- Olanzapine – weight gain
- Quetiapine – sedation

The sections below discuss the doses and side effects for aripiprazole, brexpiprazole, olanzapine, quetiapine, risperidone, and ziprasidone, when used adjunctively for unipolar major depression. Additional information about the side effects of second-generation antipsychotics is discussed separately. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

Aripiprazole — The standard dose of adjunctive aripiprazole for unipolar major depression ranges from 5 to 15 mg per day. However, patients may respond to lower doses; a randomized trial in Japanese patients found 3 mg per day effective [66]. The most common side effect is akathisia, which is dose dependent.

Doses of 5 to 20 mg per day for adjunctive aripiprazole were established in three randomized United States trials that lasted six weeks; 547 patients with major depression received active drug [36,38,67]. Aripiprazole was started at 5 mg and increased each week by increments of 5 mg per day as clinically indicated, to a maximum of 20 mg per day. The mean final dose was 11

mg per day. A subsequent United States randomized trial (n = 225) found that adjunctive aripiprazole 2 mg per day was not beneficial [68].

A subsequent six-week randomized trial compared adjunctive aripiprazole 3 mg per day with placebo in Japanese patients with treatment resistant major depression (n = 392), and found that improvement was superior with aripiprazole [66]. The difference in the efficacy of low dose aripiprazole between the United States trial and the Japanese trial may be explained by the greater prevalence of the 2D6*10 allele in Asian populations, which impairs metabolism via the CYP2D6 pathway and results in higher drug serum concentrations [69].

In a pooled analysis of two randomized trials (n = 737) lasting six weeks, the following side effects occurred in more patients who received adjunctive aripiprazole 5 to 20 mg per day than in patients who received placebo [50]:

- Akathisia (25 versus 4 percent of patients)
- Restlessness (12 versus 2 percent)
- Insomnia (8 versus 3 percent)
- Blurred vision (6 versus 1 percent)

The rate of akathisia in the two, fixed, low dose trials of aripiprazole was as follows:

- United States trial that compared aripiprazole 2 mg per day with placebo (15 versus 13 percent) [68]
- Japanese trial that compared aripiprazole 3 mg per day with placebo (14 versus 4 percent) [66]

Mean weight gain in the two trials was also greater with adjunctive aripiprazole than placebo (1.7 versus 0.4 kg) [50]. In an observational study of 994 patients with major depression who received adjunctive aripiprazole for up to 52 weeks, the mean weight gain was 4.4 kg [54]. However, one randomized trial found that although patients with late life depression gained more weight with adjunctive aripiprazole than placebo, change in body fat was comparable for the two groups, suggesting cardiometabolic risk was not affected [34].

Brexpiprazole — The dose of adjunctive brexpiprazole for unipolar depression is 1, 2, or 3 mg per day; however, 2 and 3 mg may be more efficacious than 1 mg. The most common side effects include weight gain and akathisia.

The dose of add-on brexpiprazole was established in two randomized trials that lasted six weeks; 599 patients received active drug [31,32]. However, on certain outcome measures (eg, mean reduction of depression rating scale scores), the dose of 1 mg per day was not statistically

different from placebo, whereas brexpiprazole 2 mg per day and 3 mg per day were. On other outcome measures (eg, proportion of patients who improved more than 50 percent from baseline), all three doses of brexpiprazole were superior to placebo.

Brexpiprazole is started at a dose of 0.5 mg per day for the first week of treatment, and is then titrated up to a dose of 1 mg per day for week two [31,32]. Subsequently, the dose can be increased directly to either 2 mg per day or 3 mg per day.

Weight gain during six weeks of treatment is greater with adjunctive brexpiprazole than placebo (approximately 1.5 versus 0.3 kg) [31,32].

Brexpiprazole also appears to cause dose-dependent akathisia [31,32]:

- Placebo – 2 percent of patients
- Brexpiprazole 1 mg/day – 4 percent
- Brexpiprazole 2 mg/day – 7 percent
- Brexpiprazole 3 mg/day – 14 percent

Cariprazine — The target dose of cariprazine is 1.5 to 3 mg/day [70]; however, doses of 4.5 mg/day may be indicated [33]. The most common side effects are akathisia, insomnia, and nausea [33,70].

The starting dose of adjunctive cariprazine is 1.5 mg/day [33,70]. If patients do not show improvement after two weeks and are tolerating the drug, the dose can be titrated up to 3 mg/day. Depending upon response and tolerability, the dose can be increased to 4.5 mg/day; however, rates of akathisia up to 22 percent have been reported at this dose [33].

The dose of adjunctive cariprazine was evaluated in an eight-week randomized trial, which enrolled patients with unipolar major depression (n = 819) who had an inadequate response to their current antidepressant; patients were randomly assigned to add-on cariprazine 1 to 2 mg/day, cariprazine 2 to 4.5 mg/day, or placebo [33]. The mean daily dose in the lower cariprazine dose group was 1.4 mg/day, and in the higher dose group, 2.6 mg/day. Improvement of depression was greater with cariprazine 2 to 4.5 mg/day than placebo, whereas improvement with cariprazine 1 to 2 mg/day and placebo was comparable. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received cariprazine 2 to 4.5 mg/day or cariprazine 1 to 2 mg/day, compared with patients who received placebo (49 and 48 versus 38 percent).

A six-week trial enrolled 757 patients with unipolar major depression who had an inadequate response to their antidepressant, and found that 1.5 mg of cariprazine added to their

antidepressant was more effective than placebo, but 3.0 mg/day was not more effective [71].

Adverse effects observed with adjunctive cariprazine 1.5 to 4.5 mg/day and placebo included the following [33,71,72]:

- Akathisia – 5 to 22 percent of patients
- Insomnia – 6 to 14 percent
- Nausea – 5 to 13 percent
- Fatigue – 4 to 10 percent
- Somnolence – 5 to 10 percent
- Tremor – 2 to 8 percent
- Weight gain ≥7 percent of baseline weight – 2 to 3 percent

Olanzapine — The dose of adjunctive olanzapine for unipolar major depression ranges from 5 to 20 mg per day. The most common side effect is weight gain.

The dose of adjunctive olanzapine was established in five randomized trials that lasted 8 or 12 weeks; 639 patients with major depression received active drug [51,62,73,74]. Olanzapine was generally started at 6 mg per day and increased every two weeks by increments of 6 mg per day as clinically indicated, to a maximum of 18 mg per day. The mean final dose was approximately 9 mg per day.

In a pooled analysis of two randomized trials (n = 401), side effects that occurred in significantly more patients who received adjunctive olanzapine than in those who received placebo included [51]:

- Weight gain (35 versus 7 percent of patients)
- Increased appetite (32 versus 6 percent)
- Dry mouth (29 versus 9 percent)
- Somnolence (18 versus 5 percent)
- Peripheral edema (12 versus 1 percent)
- Hypersomnia (11 versus 2 percent)

Compared with placebo, adjunctive olanzapine caused a significantly greater increase in [51]:

- Weight (4.9 versus 0.4 kg)
- Prolactin serum level (3.4 versus 0.9 mcg/L)
- Total cholesterol (15.1 versus 0.8 mg/dL)

Quetiapine — The dose of adjunctive quetiapine extended release for unipolar major depression is 300 or 150 mg per day. The 300 mg dose is slightly more efficacious, but

discontinuation from treatment is nearly 75 percent higher [35]. Use of the immediate release formulation is reasonable [75]. The most common adverse effects with either formulation are dry mouth and sedation.

The dose of adjunctive quetiapine extended release was established in two randomized trials that lasted six weeks; 627 patients with major depression received a fixed dose of quetiapine extended release 150 or 300 mg per day [35]. A trial of adjunctive quetiapine immediate release found that a mean dose of 182 mg per day was efficacious (29 patients received quetiapine) [75].

In a pooled analysis of two randomized trials (n = 936), side effects that occurred in more patients who received adjunctive quetiapine extended release 300 or 150 mg per day than placebo included [35]:

- Dry mouth (40 and 27 versus 8 percent of patients; not tested statistically)
- Somnolence (26 and 23 versus 4 percent)
- Sedation (17 and 13 versus 4 percent)
- Dizziness (12 and 11 versus 6 percent)
- Fatigue (11 and 14 versus 4 percent)
- Constipation (11 and 6 versus 4 percent)

Over six weeks, mean weight gain for adjunctive quetiapine 300 mg per day was 1.3 kg, quetiapine 150 mg per day was 0.9 kg, and placebo was 0.2 kg (not tested statistically) [35].

Hepatotoxicity due to quetiapine has been reported [76,77], including a fatal case in an older adult patient who received 25 mg per day for nine days to treat agitation and insomnia [78].

Risperidone — The dose of adjunctive risperidone for unipolar major depression ranges from 0.25 to 3 mg per day. The most common side effect is sedation and dry mouth, but both rates appear to be low.

The dose of adjunctive risperidone was established in three randomized trials that lasted between four and eight weeks; 213 patients with major depression received active drug [37,79,80]. Risperidone was started at 0.25 or 0.5 mg per day and generally increased by increments of 0.25 to 1 mg per day every several days as clinically indicated; the usual final dose was 1 to 1.5 mg per day.

In the largest randomized trial of adjunctive risperidone (n = 268), side effects that occurred in more patients who received risperidone than placebo included [37]:

- Somnolence (5 versus 2 percent of patients; not tested statistically)

- Dry mouth (5 percent versus 1 percent)
- Weight gain (4 percent versus 2 percent)
- Insomnia (4 percent versus 2 percent)

Over six weeks, mean weight gain was higher with adjunctive risperidone than placebo (1.3 versus 0.1 kg; not tested statistically).

Ziprasidone — The dose of adjunctive ziprasidone for unipolar major depression is 20 to 80 mg twice per day. The most common side effect is somnolence and fatigue.

The dose of add-on ziprasidone was established in an eight-week randomized trial; 71 patients with major depression who were treated with escitalopram received active drug [30]. Ziprasidone was started at 20 mg twice per day and increased each week by 20 mg twice per day as clinically indicated to a maximum of 80 mg twice per day; following at least one dose increase, clinicians could lower the dose to address adverse side effects. The possible dose range was thus 20 to 80 mg twice per day and the total mean daily dose was approximately 100 mg per day.

In the randomized trial (n = 139 patients), side effects that occurred in more patients who received adjunctive ziprasidone than placebo included [30]:

- Somnolence/fatigue (34 versus 12 percent of patients)
- Muscle twitching (11 versus 1 percent)
- Irritability (10 versus 1 percent)
- Anxiety/agitation (6 versus 0 percent)

In addition, weight gain was greater with active drug than placebo (3.5 versus 1.0 kg), and akathisia occurred in twice as many patients with ziprasidone than placebo (15 versus 7 percent).

It is not clear if ziprasidone causes clinically meaningful QTc prolongation. The randomized trial excluded patients with significant cardiac conduction problems (eg, atrial fibrillation, atrioventricular block, or prolonged QTc or QRS intervals), as well as patients with abnormal serum concentrations of potassium or magnesium [30]. There was a trend for a greater increase in QTc with ziprasidone than placebo (p = 0.06); ziprasidone led to a mean increase in QTc of 8.8 msec [30,81]. One patient treated with adjunctive ziprasidone discontinued treatment due to a QTc interval >500 msec.

COMBINATION TREATMENT FOR PSYCHOTIC DEPRESSION

Unipolar major depression with psychotic features (ie, delusions or hallucinations) is often treated with an antidepressant plus an antipsychotic, which is consistent with practice guidelines [16-18]. The acute and maintenance treatment of unipolar psychotic depression is discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment" and "Unipolar major depression with psychotic features: Maintenance treatment and course of illness".)

MONOTHERAPY FOR NONPSYCHOTIC DEPRESSION

Second-generation antipsychotic monotherapy may be efficacious for nonpsychotic unipolar major depression, and thus an option when switching from an ineffective treatment regimen. However, these drugs can cause many side effects (table 2), which are discussed separately. (See 'Medication doses and side effects' above and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

Lurasidone — Lurasidone monotherapy may be beneficial for unipolar major depression with mixed features. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Depression with mixed features'.)

Quetiapine — Quetiapine monotherapy can provide a small benefit for patients with major depression:

- A pooled analysis of four randomized trials (lasting six or eight weeks) compared quetiapine extended release (50, 150, or 300 mg per day) with placebo in 1752 patients with nonpsychotic unipolar major depression who were either untreated or did not respond satisfactorily to one antidepressant trial [4]. Remission occurred in more patients who received quetiapine than placebo (37 versus 30 percent); quetiapine thus provided one more remission than placebo for every 15 patients treated with each regimen. In a subsequent trial (not included in the pooled analysis), outcomes with quetiapine and with placebo were comparable [82].

- An open-label, six-week trial enrolled patients (n = 675) with unipolar major depression who, by history, did not respond to at least one antidepressant, and randomly assigned them to quetiapine monotherapy (300 mg/day), add-on quetiapine (300 mg/day), or add-on lithium (0.6 to 1.2 mmol/L) [46]. Remission with quetiapine monotherapy, add-on quetiapine, and add-on lithium was comparable (24, 32, and 27 percent of patients). In addition, discontinuation of treatment due to adverse events appeared to be comparable for the three groups (12, 10, and 8 percent).

- Another trial compared quetiapine monotherapy with placebo for late-life unipolar depression. (See "Diagnosis and management of late-life unipolar depression", section on 'Quetiapine monotherapy'.)

However, the four trials in the pooled analysis used either fixed or semifixed doses, which may underestimate differences that are achieved with a flexible dose schedule that more closely reflects clinical practice [83]. As an example, a subsequent randomized trial (also not included in the pooled analysis) using flexible doses compared quetiapine extended release with placebo in older patients, and found a larger benefit than was seen in the pooled analysis. (See "Diagnosis and management of late-life unipolar depression", section on 'Quetiapine monotherapy'.)

Although these findings indicate that quetiapine extended release has some utility for major depression, ongoing concerns remain about safety issues and side effects, especially with long term treatment. Side effects observed in the randomized trials included dry mouth, sedation, dizziness, fatigue, increased appetite, weight gain, constipation, and blurred vision [19-21,84].

Other drugs — Sulpiride appears to be effective for major depression, and amisulpride may be as well:

- A six-week randomized trial compared sulpiride (not available in the United States) with placebo as monotherapy in 171 patients with mild to moderate unipolar major depression [85]. Reduction of depressive symptoms was significantly greater in patients who received sulpiride (mean dose 181 mg per day). The type and frequency of side effects were generally comparable, except that serum prolactin was abnormally high in 50 percent of the patients treated with sulpiride.

- An eight-week randomized trial found that amisulpride (50 mg per day) and paroxetine (20 mg per day) were comparable as monotherapy in 272 patients with unipolar major depression [86]. However, the lack of a placebo arm and low fixed dose of both treatments undermine the trial's validity.

Sulpiride is not available in the United States (see "Sulpiride: International drug information (concise)"). Although amisulpride is available in the United States as an intravenous antiemetic, it is not available as an oral formulation for use in psychiatric disorders.

Olanzapine monotherapy may be as efficacious as antidepressant monotherapy for remission of unipolar major depression, but increases in prolactin and weight gain are greater with olanzapine than with antidepressants [27].

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: Depressive disorders".)

SUMMARY

- **Indications** – In unipolar major depression, second-generation antipsychotics are indicated for patients with nonpsychotic depression that does not respond sufficiently to antidepressant monotherapy (the antipsychotic is generally added to the same antidepressant), as well as psychotic depression (the antipsychotic is started concurrently with an antidepressant). Also, second-generation antipsychotic monotherapy may be efficacious for nonpsychotic depressed patients. (See 'Indications' above and 'Adjunctive treatment for nonpsychotic depression' above and 'Combination treatment for psychotic depression' above and 'Monotherapy for nonpsychotic depression' above.)

- **Efficacy**

  - **Acutely ill patients** – The efficacy of aripiprazole, brexpiprazole, cariprazine, olanzapine, quetiapine, risperidone, and ziprasidone appear to be comparable for short-term augmentation of an antidepressant that has not adequately treated an episode of major depression. Much of the benefit occurs within the first two weeks of treatment. Adjunctive second-generation antipsychotics may be effective for patients with either a minimal response to antidepressant monotherapy or a partial response. Clinicians can select a particular antipsychotic based upon its secondary clinical effects. (See 'Acute phase' above.)

  - **Remitted patients** – For patients with unipolar major depression who have failed multiple treatment regimens and then responded to an adjunctive second-generation antipsychotic that is well tolerated, it is reasonable to continue the antipsychotic to prevent relapse. (See 'Maintenance phase' above.)

- **Safety issues** – Safety issues with adjunctive second-generation antipsychotics include the metabolic syndrome, neuroleptic malignant syndrome (NMS), and tardive dyskinesia. (See 'Safety issues' above.)

- **Doses and adverse effects** – The dose of an adjunctive second-generation antipsychotic for nonpsychotic unipolar major depression is often lower than the dose used for

schizophrenia or bipolar disorder. Short-term use of adjunctive atypical antipsychotics for depression is usually well tolerated; however, adverse effects such as akathisia, weight gain, and sedation lead patients to discontinue treatment at significantly greater rates than placebo. (See 'Medication doses and side effects' above.)

Topic 14688 Version 43.0

→