Treatment-resistant depression
Are atypical antipsychotics effective and safe enough?

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Adjunctive 'atypicals' may improve chronic unipolar depression; deciding when the benefits outweigh the risks is the clinical challenge.

Adding second-generation antipsychotics (SGAs) may boost the effectiveness of antidepressants in treatment-resistant unipolar major depression. Exactly when to try SGAs remains unclear, however, given their potential for adverse effects.

Major depression often is severe and chronic, and many patients remain ill even after multiple rounds of treatment. For patients without psychosis, where do SGAs fit into an algorithm for treatment-resistant depression?

This article examines the evidence on antipsychotic augmentation and discusses issues to consider—effectiveness, adverse effects, therapeutic dosages, and the patient's quality of life—in making your clinical decisions.

ANTIDEPRESSANTS ALONE
An optimal trial. Most depressed patients do not experience full response after initial antidepressant treatment, even with optimal therapeutic trials. An optimal trial means maintaining the maximum tolerated dosage within the antidepressant's typical therapeutic range for at least 3

Therapeutic suggestions when an SSRI does not lead to remission*

Pharmacotherapy	Example	Recommended dosing
Monotherapy	An SNRI such as:	
	Duloxetine	30 to 120 mg/d
	Venlafaxine XR	150 to 375 mg/d
Combination therapies with SSRIs	Bupropion	200 to 400 mg/d
	Buspirone	30 to 60 mg/d
Augmentation	Lithium	900 to 1,200 mg/d
	Thyroid hormone	25 mcg/d
	Pindolol	5 to 30 mg bid
	Estrogen (such as 17a-estradiol)	100 mcg/d
Switch to another antidepressant class	**Tricyclic**	
	Imipramine	150 to 250 mg/d*
	Nortriptyline	75 to 200 mg/d*
	Desipramine	150 to 250 mg/d*
	MAOI	
	Phenelzine	30 to 60 mg/d
	Tranylcypromine	20 to 60 mg/d
	Selegiline (patch)	9 to 12 mg/patch/day

* Suggestions are not listed in stepwise order
MAOI: monoamine oxidase inhibitor
SNRI: serotonin-norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor

weeks.[1] Reported remission rates from initial and second-line treatments include:

- one-third of patients after a vigorous initial trial of citalopram in a National Institute of Mental Health study[2]
- 20% to 30% of patients given citalopram plus bupropion or buspirone[3] or switched to bupropion, sertraline, or venlafaxine[4]
- 50% of patients treated for depression in a primary care practice during the first 2 years after an initial antidepressant prescription.[5]

Among patients who do achieve remission from initial therapy, many eventually relapse to major depression or show a recurrence of depressive symptoms.[6]

Subsequent options. In addition to various monotherapies and combinations, many options have been proposed for managing nonresponse to initial antidepressant therapy (*Table 1*). These include:

- augmenting with lithium, thyroid hormone, pindolol, or estrogen
- switching to a drug in another therapeutic class, such as a tricyclic antidepressant or monoamine oxidase inhibitor
- adding cognitive-behavioral therapy.[7]

Yet many patients remain depressed after these treatments are tried, with a reduced quality of life and at high risk for suicide or long-term disability (*Box 1, page 35*).[6,8] For these patients, accumulating

evidence suggests that at least some SGAs can be effective for acute treatment of unipolar depression that does not respond to antidepressants.

ATYPICALS FOR UNIPOLAR DEPRESSION

Why atypicals? Researchers are investigating the use of SGAs in treatment-resistant mood disorders because of these drugs' unique psychopharmacologic properties (*Box 2, page 36*).[9-11]

Except for clozapine, all available SGAs—aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone—are FDA-approved for acute bipolar mania. Evidence also strongly supports the benefits of quetiapine[12] and the fixed-dose olanzapine/fluoxetine combination[13] for bipolar depression. Olanzapine/fluoxetine—originally studied for use in treatment-resistant unipolar depression—is approved for bipolar depression.[14]

Robust response. An uncontrolled case series first suggested that an SGA might help treat unipolar depression after initial selective serotonin reuptake inhibitors (SSRIs) fail to achieve remission. Ostroff and Nelson[15] enrolled 8 outpatients (5 men, 3 women, ages 36 to 75) with nonpsychotic unipolar major depression that did not respond to initial fluoxetine or paroxetine. Patients had been taking fluoxetine, 20 to 40 mg/d, for 6 weeks to 4 months or paroxetine, 10 to 30 mg/d, for 2 to 8 weeks.

Patients reported a robust clinical effect within days after risperidone, 0.5 to 1.0 mg/d, was added to the SSRIs. Depression symptoms dropped to remission levels within 1 week, as measured by baseline and follow-up Hamilton Rating Scale for Depression (HAM-D) scores.

Olanzapine/fluoxetine. Our group subsequently enrolled 28 nonpsychotic patients with unipolar depression in a double-blind, placebo-controlled trial.[14] We first treated these patients—who had not responded adequately to an SSRI or an antidepressant from another class—with open-label fluoxetine, up to 60 mg/d. Those whose scores on depression rating scales improved by ≥ 30% were

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Box 1

Remission: Why it's the goal of antidepressant therapy

Depression is often chronic and disabling. Selective serotonin reuptake inhibitors (SSRIs) are the mainstay of treatment, but recent data suggest that:

- few patients achieve therapeutic remission with initial SSRIs
- relapse or recurrence after remission is common.[6]

Clinically, this means psychiatrists contend with treatment resistance in nearly all patients with major depression.

Chronic, inadequately treated depression has a pervasive, adverse effect on patients' quality of life, impairing the ability to work and perform social roles such as parenting. Even when an antidepressant produces partial response, considerable impairment remains. Depressed patients who do not achieve full therapeutic remission remain in this partially remitted, disabled state throughout treatment.[8]

Aggressive and persistent management is the key to effectively treating major depression.

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excluded from the double-blind phase, when we randomly assigned the remaining patients to:

- olanzapine, mean 12.5 mg/d, plus placebo (n=8)
- a continuation of fluoxetine, mean 52 mg/d, plus placebo (n=10)
- or olanzapine/fluoxetine, mean 13.5/52 mg/d (n=10).

Continuing fluoxetine produced essentially no additional therapeutic benefit. Olanzapine plus placebo showed an initial effect, but patients relapsed to baseline depression symptoms after 3 weeks. This is consistent with residual fluoxetine

Antidepressant-like effects included in SGAs' 'atypical' qualities

Second-generation antipsychotics (SGAs) differ from first-generation antipsychotics (FGAs) in their putative mechanisms of action.

FGAs' antipsychotic effects depend largely on central dopamine type 2 (D2) receptor blockade. Their additional receptor-binding characteristics—blocking cholinergic, histamine, and alpha adrenergic receptors—appear to confer side effects but no added therapeutic benefit.[9]

SGAs bind weakly to D2 receptors and in varying degrees to serotonin (5-HT) receptors, including 5-HT subtypes 1A, 2A, 2C, 5, 7, and others. The SGAs also have other transmitter effects.[10] On balance, the SGAs' effects are more complex than those of the FGAs.

SGAs are called "atypical" because their beneficial and adverse clinical actions do not follow the FGAs' usual pattern. FGAs' relative potency in reducing psychosis is proportional to the propensity to cause extrapyramidal symptoms (EPS). Both the clinical effect and EPS are functions of D2 receptor blockade.[11] In contrast, clozapine—the prototypical SGA—is a potent antipsychotic that exerts essentially no EPS.

Compared with FGAs, clozapine's more complicated psychopharmacology has been shown to produce an enhanced effect on negative, cognitive, and mood symptoms in some patients with schizophrenia.[10]

levels during that period after patients stopped taking the SSRI. The olanzapine/fluoxetine combination resulted in significantly greater improvement in depressive symptoms during the 8-week study, compared with either monotherapy.

Final depression remission rates (HAM-D score ≤ 8 for 2 weeks) were:

- 60% with olanzapine/fluoxetine
- 25% with olanzapine alone
- 20% with continuation fluoxetine.

The olanzapine/fluoxetine combination's benefits were maintained during a subsequent 8-week extension.

Until recently, researchers had been unable to replicate these results or extend this study in larger populations because of high response rates in the monotherapy treatment groups.[16,17] In May 2006, however, Thase et al[18] presented data from a large-scale replication trial that confirmed the finding of a more robust effect with fixed-dose olanzapine/fluoxetine in unipolar major depression, compared with olanzapine or fluoxetine monotherapy.

Ziprasidone. Case series, open-label trials, and blinded controlled studies of other SGAs have produced varying results.[19,20] Dunner et al[20] conducted an 8-week, randomized, open-label trial of ziprasidone augmentation in 64 patients who had not responded to an SSRI. Patients were randomly assigned to:

- sertraline, 100 to 200 mg/d
- sertraline plus ziprasidone, 80 mg/d
- or sertraline plus ziprasidone, 160 mg/d.

Depressive symptoms improved in all groups, based on mean Montgomery-Åsberg Depression Rating Scale scores (–4.5 points with sertraline alone, –6.0 points with sertraline plus ziprasidone, 80 mg/d, and –8.3 points with sertraline plus ziprasidone, 160 mg/d). Differences in these scores were not statistically significant.

Risperidone. One three-phase study[21] evaluated the long-term efficacy of adding risperidone to citalopram in 489 patients with treatment-resistant depression. The design was:

- phase 1: 4 to 6 weeks of open-label citalopram, 20 to 60 mg/d (N=489)
- phase 2: 4 to 6 weeks of citalopram plus open-label risperidone, 0.25 to 2 mg/d (N=386)

- phase 3: 24 weeks of citalopram plus double-blind risperidone or placebo (N=241).

The study's primary outcome was time to relapse during phase 3. Phase 1 patients whose HAM-D scores improved <50% with citalopram entered phase 2. With open-label risperidone augmentation, depression remitted in 243 of patients (63%), and 241 of them entered phase 3.

Median time to relapse in phase 3 was 102 days with risperidone augmentation and 85 days with placebo—not a statistically significant difference. Relapse rates were 53.3% with risperidone and 54.6% in the control group. These results suggest that risperidone had an initial acute effect that was not sustained.

In another study,[22] 463 depressed patients received an optimized antidepressant trial. The 274 who did not respond sufficiently were randomly assigned to risperidone, 1 to 2 mg/d, or placebo for 6 weeks. Mean HAM-D scores fell from 24.2 to 15.2 in the risperidone group and from 24.6 to 17.5 in the control group—a modest but statistically significant difference in favor of risperidone. The baseline-to-endpoint change in this study is similar to that reported in a trial of risperidone, 1 to 4 mg/d, plus paroxetine, 20 to 40 mg/d, in bipolar depression.[23]

Shelton[24] compared the effectiveness of adding risperidone or bupropion to SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) for 6 weeks. Risperidone and bupropion were similarly effective as augmentation, but risperidone had a more rapid effect—producing statistically significant greater benefits within the first week of treatment.

Aripiprazole. Two open-label trials showed that aripiprazole combined with SSRIs exerts generally beneficial effects in treatment-resistant depression.[25,26] Simon and Nemeroff[25] began by adding aripiprazole at 10 mg/d, but emerging akathisia prompted them to reduce the starting dosage to 2.5 mg/d.

Barbee et al[27] reported the results of a retrospective case series of aripiprazole augmentation in depressed patients who had not responded adequately to multiple medication trials, including SGAs. Fourteen of 30 patients (46.7%) were rated "much improved" or "very improved" with added aripiprazole, based on Prospective Global Assessment of Functioning and Clinical Global Impressions-Improvement scores. But 9 patients (30%) did not complete the full course of therapy, and 6 of the 14 responders (42.9%) relapsed while taking aripiprazole. The net response rate across 6 weeks was 27%.

Although this study involved only aripiprazole, the results suggest that trying a second SGA may not be more effective after a first SGA fails to improve treatment-resistant depression.

Quetiapine. A 9-week, open-label, variable-dose study of 11 patients[28] first suggested that augmenting SSRIs with quetiapine could improve residual anxiety in resistant depression. Subsequently, 112 patients with major depression and anxiety were randomly assigned to single-blind treatment with paroxetine, ≥ 60 mg/d, with or without quetiapine, ≥ 200 mg/d. After 8 weeks, the 58 patients receiving

> Trying another SGA after the first one fails has not been shown to improve treatment response

Table 2

Recommended dosing of SGAs to augment antidepressant therapy

Medication	Therapeutic range (mg/d)
Aripiprazole	5 to 30
Olanzapine	5 to 20
Quetiapine	100 to 400
Risperidone	2 to 4
Ziprasidone	80 to 160

quetiapine augmentation showed greater improvement than the 54 receiving SSRI monotherapy, based on Hamilton Anxiety Scale (HAM-A) and HAM-D scores.[29]

Adding quetiapine to antidepressant therapy was then examined in a randomized, placebo-controlled trial by McIntyre et al.[30] Fifty-eight patients with unipolar depression who had not responded adequately after 6 weeks of SSRI or SNRI therapy were randomly assigned to quetiapine, 50 to 600 mg/d (mean dose 202±93 mg/d) or placebo for 8 weeks. Adjunctive quetiapine was significantly more effective than placebo, as measured by HAM-D scores. Patients receiving quetiapine also showed significantly better HAM-A scores at all points except week 8.

The dropout rate was relatively high for both groups—11 of 29 (38%) receiving quetiapine and 13 of 29 (45%) receiving placebo. The main reasons for discontinuation were side effects with quetiapine (sedation, dry mouth, and weight gain) and lack of effect with placebo.

☑ INSTANT POLL
When two SSRI trials have failed, at what point would you add a second-generation antipsychotic?

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These results are similar to those of another double-blind, placebo-controlled trial,[31] in which 32 patients with SSRI/SNRI-resistant depression received adjunctive quetiapine, 200 to 400 mg/d (mean 268 mg/d) or placebo for 8 weeks.

Though small, these studies indicate that quetiapine may be effective as augmentation for treatment-resistant unipolar depression. Controlled data from a larger study are needed.

Discussion. Because of insufficient data, we do not know if SGAs are equivalent when used to augment antidepressant therapy in unipolar major depression. Olanzapine has been studied more than other SGAs in treatment-resistant depression and has shown efficacy in several—but not all—short- and long-term augmentation trials. Evidence on other SGAs is limited, and no head-to-head comparisons have been reported.

ADVERSE EFFECTS
Some SGAs may be effective in treatment-resistant depression, but any discussion of using them must also include their potential for adverse effects.

Weight gain and subsequent metabolic syndrome have been associated with olanzapine and—to a lesser degree—with quetiapine and risperidone. Ziprasidone and aripiprazole have relatively little effect on patients' weight.

Extrapyramidal symptoms. All SGAs carry a risk of tardive dyskinesia. The risk is lower with SGAs than with first-generation antipsychotics (FGAs) but is an important clinical consideration.[32]

Hyperprolactinemia. Risperidone has been associated with an elevated risk of hyperprolactinemia, although less than that associated with FGAs.[33] This risk does not appear to be a problem with quetiapine[34] and aripiprazole;[35] it is low with olanzapine (except at higher dosages);[36] and the prolactin increase associated with ziprasidone may resolve within the first month of treatment.[37]

PRESCRIBING RATIONALE

'Overcautious' treatment. Even with careful management of side effects, SGAs are not preferred to strategies such as switching antidepressants or adding bupropion for treatment-resistant unipolar depression. But do not exclude SGAs solely because of their potential for adverse effects.

I am concerned about anecdotal reports of overcautious clinicians basing medication choices largely on safety—and, by extension, legal—considerations rather than on effectiveness. Certainly, safety concerns should prevail when two options are equally effective. But we do our patients no service by selecting ineffective drugs just because they have a low potential for adverse effects or by dosing effective drugs below the therapeutic range (*Table 2, page 38*).

When a drug is effective and may be the best choice for the patient, the question becomes, "Can I manage the potential for adverse effects?" When prescribing SGAs, it is important to monitor patients' weight and serum lipid and glucose levels and regularly to look for abnormal involuntary movements.

An important question remains: Where do SGAs belong in the hierarchy of treatment options? Unfortunately, treatment guidelines for depression do not typically mention antipsychotics. Because of relative safety issues, two trials of monotherapies of different classes and, perhaps, combination therapy with bupropion would come before SGAs. However, it remains unclear exactly where.

SGAs probably belong ahead of electroconvulsive therapy or vagal nerve stimulation. But should they come before augmentation with lithium or thyroid hormone? Or, for that matter, trials of tricyclics or monoamine oxidase inhibitors?

Unfortunately, the available evidence provides little guidance. For a list of therapeutic algorithms developed for treatment-resistant depression, see *Related resources*.

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For treatment-resistant depression, limited evidence supports augmenting antidepressants with second-generation antipsychotics (SGAs). Risk of adverse effects—particularly tardive dyskinesia—has muted enthusiasm for SGA use, however. Do not add an SGA early in treatment, but consider this option if other treatments fail to relieve depressive symptoms.

BottomLine

Related resources

Algorithms for treatment-resistant depression

▸ Trivedi MH, Kern JK, Grannemann BD, et al. A computerized clinical decision support system as a means of implementing depression guidelines. *Psychiatr Serv* 2004;55(8);879-85.

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DRUG BRAND NAMES

Aripiprazole • Abilify
Bupropion • Wellbutrin
Buspirone • BuSpar
Citalopram • Celexa
Clozapine • Clozaril
Desipramine • Norpramin
Duloxetine • Cymbalta
Imipramine • Tofranil
Lithium • various
Nortriptyline • Pamelor
Olanzapine • Zyprexa

Olanzapine/fluoxetine • Symbyax
Phenelzine • Nardil
Pindolol • Visken
Quetiapine • Seroquel
Risperidone • Risperdal
Selegiline (patch) • EMSAM
Sertraline • Zoloft
Tranylcypromine • Parnate
Venlafaxine • Effexor
Ziprasidone • Geodon

DISCLOSURE

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