Current PSYCHIATRY

Antipsychotics for patients without psychosis?

What clinical trials support

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Controlled clinical trial results can help you make two prescribing decisions:

- Is an antipsychotic the right choice for this patient?
- If yes, which agent?

Prescribing antipsychotics off-label can be worthwhile when a patient gets better, but even then two worries remain:

- Most uses of antipsychotics for nonpsychotic illness are not evidence-based.
- This practice may expose clinicians to liability if the patient gets worse.

Consider the use of second-generation antipsychotics (SGAs) to manage acute behaviors in patients with dementia. The FDA ordered a black box warning in 2005 that SGAs may increase mortality risk in older patients. In October, the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) reported that SGAs' side effects offset their benefits when compared with placebo (*see page 49*).[1]

What do you do when FDA-approved drugs fail to help your patient with dementia, unipolar depression, anxiety disorders, or other nonpsychotic symptoms, and SGAs may be the next consideration? The answers lie in managing side effects and knowing which antipsychotic uses are supported by data from controlled clinical trials, which we review here.

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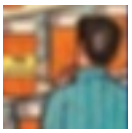

Box 1

Why SGAs are widely used in nonpsychotic disorders

- FGAs showed efficacy for nonpsychotic disorders
- SGAs are associated with a lower risk of EPS and tardive dyskinesia at therapeutic dosages, compared with FGAs
- Many patients fail to respond adequately to medications approved for their illnesses
- Evidence on SGAs' efficacy in nonpsychotic disorders has grown substantially in the past 10 years.

EPS: extrapyramidal symptoms
FGA: first-generation antipsychotic
SGA: second-generation antipsychotic

PRESCRIBING CONSIDERATIONS

For a variety of reasons (*Box 1*), SGAs have rapidly assumed a major role in treating nonpsychotic disorders. Thirty-one percent of psychotropics are dispensed off-label,[2] and Buckley[3] reported in a 3-state survey that 70% of SGA prescriptions were written for indications other than schizophrenia.

Using antipsychotics for nonpsychotic symptoms is a longstanding clinical practice. In schizophrenia patients, antipsychotics have been shown to improve psychotic and nonpsychotic symptoms: agitation, violence, negative symptoms, social isolation, depression, suicidality, anxiety, insomnia, poor appetite, compulsions, cognition, smoking, alcohol and drug use, polydipsia, tardive dyskinesia, and tardive dystonia. Some clinicians may view these reports as evidence that antipsychotics might relieve these symptoms in patients with nonpsychotic disorders as well, but the issue is more complicated than that (*Box 2*).[4]

Caveats. SGAs do offer clinicians unique tools; no other class of psychotropics can claim efficacy in psychotic disorders, bipolar disorder, depression, and other disorders we describe in this review. On the other hand:

- Although some SGAs are approved for bipolar disorder and one was recently approved to treat irritability in autism (*Table 1, page 37*), most SGA uses in nonpsychotic disorders are off-label and supported by few—if any—large, randomized, controlled trials.
- Antipsychotics can cause the very symptoms they relieve, including depression, obsessive-compulsive disorder (OCD), anxiety, poorer cognition, agitation, mania, insomnia, and abnormal movements.
- Few controlled studies have compared SGAs to usual first-line treatments; most have evaluated SGAs as adjuncts to other psychotropics—such as serotonin reuptake inhibitors (SRIs)—for patients with treatment-resistant disorders.
- Published head-to-head studies have rarely compared the efficacy of various SGAs in treating nonpsychotic disorders.
- Long-term safety studies of SGAs for nonpsychotic indications have not been done.

Among the SGAs, more studies of risperidone and olanzapine have been done in nonpsychiatric disorders, compared with quetiapine, ziprasidone, or aripiprazole. Clozapine has shown positive effects in mania, aggressiveness. and tardive dyskinesia, but few controlled studies of off-label uses have been done because of clozapine's risk of agranulocytosis.

Safety issues. SGAs' safety profiles warrant caution. SGAs are less likely than first-generation antipsychotics (FGAs) to cause extrapyramidal symptoms (EPS) and tardive dyskinesia at therapeutic dosages, but they increase the risks of weight gain, diabetes, glucose intolerance, dyslipidemia, and hyperprolactinemia. Akathisia and hypotension also may occur.

Prescribing decisions. SGA's potential adverse effects complicate clinical decision-making. First

Box 2

How do antipsychotics work in nonpsychotic illness?

Second-generation antipsychotics (SGAs) show efficacy in so many psychotic and nonpsychotic disorders that a specific therapeutic action for each disorder is highly doubtful. One might ask, then: What do they improve, and how do they do it?

The complete answer is beyond current understanding, unfortunately. We do know, however, that SGAs have not shown efficacy for treating nonpsychotic disorders that first-generation antipsychotics (FGAs) did not show—except perhaps for maintenance treatment in bipolar disorder.

Calming action. The major clinical action of SGAs appears to be in calming patients, which also was the first therapeutic effect attributed to the FGA chlorpromazine. This calming effect would explain SGAs' efficacy in treating agitation, aggressiveness, anxiety, and possibly mania. Other clinical effects specific to psychosis and possibly to depression are possible.

Receptor-blocking action. SGAs' D2 and 5-HT2A receptor-blocking activity may explain much of the drugs' therapeutic effect. However, if SGAs' effect on nonpsychotic symptoms derives from their action on nondopaminergic receptors, then individual SGAs would vary widely in efficacy and pure dopaminergic agents such as amisulpride would be ineffective.

SGAs also bind at other receptor sites, and the clinical importance of this may vary from patient to patient, drug to drug, and dose to dose.[4]

you must decide whether or not to use an SGA for your patient with a nonpsychotic disorder.

Knowing, for example, that antipsychotics have been shown to increase mortality and cerebrovascular events in older patients might make

you less likely to prescribe an SGA for a patient with dementia-related agitation. No other pharmacologic treatment has shown clear efficacy for these patients, however, so other factors are important to consider, including:

- patient history and clinical characteristics
- potential side effects
- individual therapeutic response to previous medications.

If you decide to use an SGA, you then must choose among the available agents. Because head-to-head comparisons are lacking, consider data that exist for your patients' nonpsychotic indications (*Table 1, page 37, and Table 2, page 38*).

DEMENTIA

Most Alzheimer's patients—75% to 90%—experience behavioral problems during this progressive dementia. Double-blind studies have found risperidone (mean dosage ~1 mg/d) and olanzapine (mean dosage 5 to 10 mg/d) effective in reducing agitation and aggression, even in nonpsychotic patients with Alzheimer's disease or vascular dementia.[5,6] Quetiapine, ≤100 mg/d, was not more effective than placebo in reducing agitation.[7] One study comparing IM olanzapine with IM lorazepam and placebo in acute agitation found both active treatments more effective than placebo.[8]

CATIE-AD—sponsored by the National Institute of Mental Health—compared olanzapine, risperidone, and quetiapine with placebo in 421 outpatients with behavioral symptoms such as psychosis, agitation, or aggressiveness.[1] No significant differences were seen in overall effectiveness (measured as discontinuation for any cause[9]), although patients receiving olanzapine (mean dosage 5.5 mg/d) or risperidone (mean dosage 1 mg/d) had lower discontinuation rates for lack of efficacy than those receiving placebo.

Unfortunately, the results of the first phase of CATIE-AD provide no clear guidance on the therapeutic strategy to use in dementia. Its findings do suggest two secondary conclusions, however, about using SGAs for patients with dementia:

- Because quetiapine, mean dosage 56.5 mg/d, was not more effective than placebo on any measures, consider higher dosages when using this agent.
- Close attention to preventing and treating SGAs' side effects is the key to effectively treating agitation and psychosis in dementia.

Other studies. In addition to common side effects observed with SGAs, controlled data suggest that olanzapine and quetiapine can worsen cognition in older patients with dementia.[7,10] SGAs—as well as FGAs—also have been associated with increased risk of cerebrovascular events (stroke and transient ischemic attacks) and mortality in this population.[11,12]

> SGAs remain the first therapeutic option for psychosis and agitation in Alzheimer's patients

Recommendation. Nonpharmacologic interventions are an important part of treating behavioral problems in patients with dementia.[13,14] Antipsychotics—particularly SGAs—have shown efficacy for psychosis and agitation in these patients and remain the first therapeutic option. The CATIE-AD investigators recommend that clinicians evaluate potential risks and benefits of pharmacotherapy and discuss these with patients and caregivers.[1] Also:

- Consider which SGAs have the lowest risk of causing side effects for an individual patient.
- Start with low dosages and increase as needed, based on efficacy and tolerability.

BIPOLAR DISORDER

Acute mania. Five SGAs—aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone—are FDA-approved for acute mania (*Table 1*). Large double-blind studies supporting this indication

Table 1

Bipolar and other nonpsychotic indications FDA-approved for SGAs

SGA	Bipolar mania	Bipolar depression	Bipolar maintenance	Other
Aripiprazole	Acute mania or mixed episodes		Bipolar I disorder, most recent episode manic or mixed	
Clozapine				Risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorders
Olanzapine	Acute mania or mixed episodes; monotherapy or with lithium or valproate for manic episodes		Bipolar disorder maintenance monotherapy	
Olanzapine/ fluoxetine combination		Bipolar depressive episodes		
Quetiapine	Acute manic episodes; monotherapy or with lithium or valproate	Bipolar depressive episodes		
Risperidone	Acute mania or mixed episodes; monotherapy or with lithium or valproate			Irritability in autism
Ziprasidone	Acute manic or mixed episodes			

SGA: second-generation antipsychotic (oral forms)

show that SGAs have efficacy in treating mania as monotherapy and in combination with lithium or divalproex.[15] These clinical trials included patients who were not psychotic at baseline.

Antipsychotic dosages in these studies were within the ranges used in schizophrenia treatment studies. Combining an SGA with lithium or divalproex generally yields greater reductions in mania rating scale scores, higher response rates, and higher remission rates than using lithium or divalproex alone. No published study has compared SGAs with each other in mania, but differences in efficacy among these compounds are likely to be small.[16]

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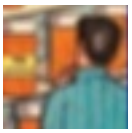

Table 2

Which SGA uses in nonpsychotic disorders are supported by evidence from published double-blind clinical trials*

SGA	Unipolar depression	OCD	Anxiety disorders	Dementia	Developmental disorders	Borderline personality disorder
Aripiprazole						Yes
Clozapine						
Olanzapine	Yes	Yes	Yes	Yes		Yes
Quetiapine		Yes				
Risperidone		Yes	Yes	Yes	Yes	
Ziprasidone						

* Not including studies of bipolar disorder
OCD: obsessive-compulsive disorder
SGA: second-generation antipsychotic

Bipolar depression. SGAs' efficacy in bipolar depression has been evaluated in double-blind studies, and quetiapine and the olanzapine/fluoxetine combination are FDA-approved for this indication.

Olanzapine plus fluoxetine was more effective in improving depressive symptoms than olanzapine alone in a double-blind study of 833 adults with depressive symptoms of bipolar I disorder, as measured by Montgomery-Åsburg Depression Rating Scale (MADRS) scores. Olanzapine alone was more effective than placebo. Mean dosages were olanzapine, 7.4 mg/d, and fluoxetine, 39.3 mg/d, in combination therapy and olanzapine, 9.7 mg/d, as monotherapy.

MADRS scores indicated that combination therapy—but not olanzapine alone—improved core depressive symptoms such as sadness, lassitude, inability to feel, and pessimistic thoughts.[17]

Quetiapine. A double-blind, placebo-controlled trial (BOLDER I) evaluated quetiapine in 542 outpatients experiencing a major depressive episode associated with bipolar I or II disorder. After 8 weeks, quetiapine at 300 or 600 mg/d was more effective than placebo in reducing depressive symptoms, as measured by MADRS score changes.

Response rates were 58% with quetiapine and 36% with placebo; remission rates were 53% with quetiapine and 28% with placebo. Most symptoms, including core depression items, improved significantly with quetiapine, compared with placebo.[18] Results of a second double-blind study (BOLDER II) have been presented at conferences but have not been fully published.

Risperidone. A smaller double-blind study compared risperidone plus placebo, paroxetine plus placebo, and risperidone plus paroxetine in 30 patients in the depressed phase of bipolar I or II disorder. Patients continued taking mood stabilizers during the study. After 12 weeks, depressive symptoms improved significantly in all three groups, with no significant differences.[19]

Maintenance therapy. Olanzapine and aripiprazole are FDA-approved for maintenance therapy in bipolar disorder (*Table 1, page 37*).

UNIPOLAR DEPRESSION

FGAs have shown efficacy in depression in multiple controlled studies.[20] SGAs have been evaluated mostly as add-on therapies in antidepressant-resistant depression.

Olanzapine. Shelton et al[21] compared olanzapine monotherapy, fluoxetine monotherapy, and combined treatment in 34 nonpsychotic, treatment-resistant depressed subjects. Olanzapine plus fluoxetine was more effective than either agent alone. A subsequent double-blind study, however, showed similar efficacy after 8 weeks among the three treatments and nortriptyline monotherapy. Patients in the double-blind trial appeared to respond more rapidly to combined treatment than to the monotherapies.[22]

Risperidone. A multiphase study of the efficacy of risperidone augmentation in treatment-resistant major depression began when 489 outpatients (2% with psychotic symptoms) received open-label citalopram, 20 to 60 mg/d. After 4 to 6 weeks, 386 nonresponders entered the augmentation phase with open-label risperidone, 0.25 to 2 mg/d. After 4 to 6 weeks of combination therapy, 241 (63%) patients whose symptoms resolved entered a double-blind discontinuation phase, in which they were randomly assigned to augmentation with risperidone or placebo, while on citalopram.

Median time to relapse during the double-blind phase was 102 days with risperidone augmentation and 85 days with placebo—not a statistically-significant difference. Relapse rates after 24 weeks were 53.3% and 54.6%, respectively.[23] This study showed that the improvement observed after adding risperidone was not sustained over time.

Quetiapine. In a prospective single-blind study, paroxetine augmented with quetiapine, 200 mg/d, was compared to paroxetine alone in major depression with anxiety.[24] Combination therapy was more effective in improving anxiety and depression symptoms.

Others. Open-label, add-on studies indicate that

aripiprazole and ziprasidone can improve treatment-resistant depression.[25-27]

ANXIETY DISORDERS

OCD. SGAs also have been investigated as augmentation therapy for patients with OCD resistant to SRIs. A single-blind study of 27 patients found adjunctive quetiapine more effective than placebo in improving OCD symptoms.[28] SGAs were more effective than placebo as augmentation therapy to SRIs for treatment-refractory OCD in double-blind, placebo-controlled studies using mean dosages of:

- risperidone, 2.2 mg/d
- olanzapine, 11 mg/d
- quetiapine, 300 mg/d.[29-31]

PTSD, others. In randomized trials, symptoms of posttraumatic stress disorder (PTSD) such as irritability, hyperarousal, and re-experiencing improved in patients treated with olanzapine or risperidone.[32,33]

In other trials:

- A small double-blind study of patients with social anxiety disorder found olanzapine monotherapy more effective than placebo.[34]
- Low-dose risperidone (mean dosage 1.1 mg/d) improved core symptoms of generalized anxiety disorder in a 5-week, double-blind, placebo-controlled trial.[35]

Recent approvals: risperidone for irritability in autism, and quetiapine for bipolar depression

- Some authors have reported clinical improvement of panic disorder with olanzapine augmentation.[36]

DEVELOPMENTAL DISORDERS

Antipsychotics represent one-third of all filled psychotropic prescriptions for individuals with pervasive developmental disorders (PDD).[37] Haloperidol and thioridazine are the only two FDA-approved FGAs for severe behavioral problems in PDD (and for hyperactivity with conduct disorders). Recently, risperidone received FDA approval for the treatment of irritability associated with autistic disorder in children.

Risperidone—the most-studied SGA in the PDD population—has shown efficacy in autism and in PDD not otherwise specified. Risperidone at dosages <3 mg/d improved repetitive behavior and aggression in adult patients.[38]

In children with autism, risperidone can improve tantrums, aggression, and self-injury. In a study of risperidone's effect on autism's core symptoms, the authors reported improvements in repetitive and stereotyped behavior but not in social relatedness or verbal communication.[39]

Double-blind studies have shown positive effects on aggression and behavioral disturbances in children with conduct disorder, oppositional defiant disorder, and other disruptive disorders, developmentally delayed adolescents, and mentally retarded subjects of various ages.[40-42] Children and adolescents appear to be more sensitive than adults to risperidone's side effects such as weight gain, EPS, and pancreatitis.

PERSONALITY DISORDERS

Antipsychotics have been recommended for paranoid ideas and psychotic-like symptoms in borderline personality disorder and in paranoid personality disorder.[43]

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Olanzapine. A 24-week, double-blind study found low-dose olanzapine (mean dosage 5.3 mg/d) more effective than placebo for anxiety, interpersonal sensitivity, paranoia, and anger/hostility in women with borderline personality disorder.[44]

In another double-blind study, 12 weeks of olanzapine therapy (mean 6.9 mg/d) was more effective than placebo for inappropriate anger in borderline personality disorder, as measured by a modified Clinical Global Impression scale.[45]

Others. Anger and hostility improved more with aripiprazole, 15 mg/d, than with placebo in an 8-week double-blind study of patients with borderline personality disorder.[46] Quetiapine, risperidone, ziprasidone, and clozapine have shown efficacy in open-label studies and case reports.

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Bottom Line

Second-generation antipsychotics have shown benefit in nonpsychotic disorders such as behavioral problems associated with dementia, unipolar depression, anxiety disorders, and other diagnoses. When deciding whether to use antipsychotics for patients without psychosis, consider available double-blind controlled data and the patient's risk of side effects.

continued

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DRUG BRAND NAMES

Aripiprazole • Abilify
Chlorpromazine • Thorazine
Citalopram • Celexa
Clozapine • Clozaril
Divalproex • Depakote
Fluoxetine • Prozac
Haloperidol • Haldol
Nortriptyline • Pamelor, Aventyl
Olanzapine • Zyprexa
Olanzapine/fluoxetine • Symbyax
Paroxetine • Paxil
Quetiapine • Seroquel
Risperidone • Risperdal
Thioridazine • Mellaril
Ziprasidone • Geodon

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