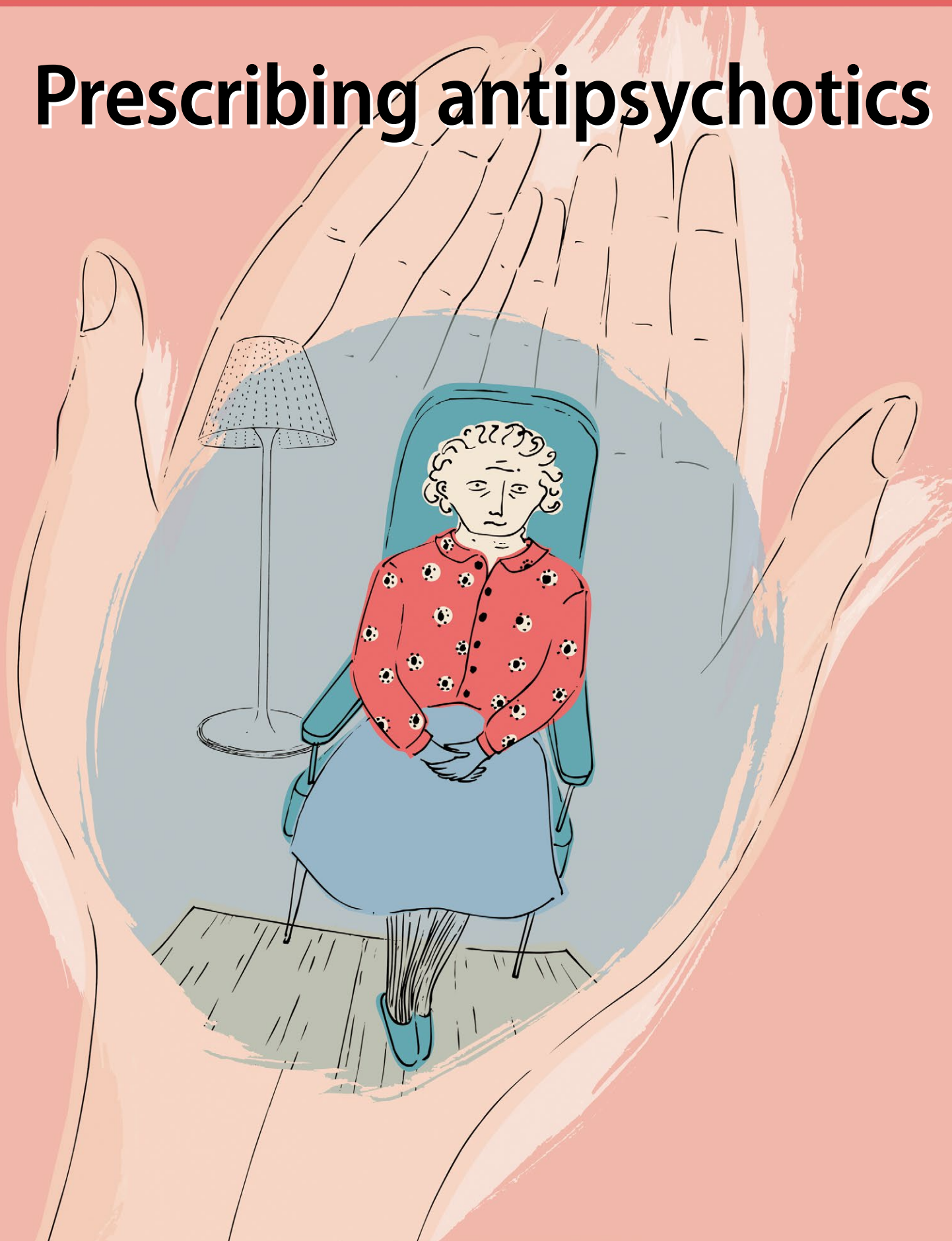


FIRST OF 3 PARTS

Prescribing antipsychotics



in geriatric patients:

Focus on schizophrenia and bipolar disorder

Avoid adverse effects by using the lowest effective dose of a second-generation agent

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Antipsychotics are FDA-approved as a primary treatment for schizophrenia and bipolar disorder and as adjunctive therapy for major depressive disorder. In the United States, approximately 26% of antipsychotic prescriptions written for these indications are for individuals age >65.¹ Additionally, antipsychotics are widely used to treat behavioral symptoms associated with dementia.¹ The rapid expansion of the use of second-generation antipsychotics (SGAs), in particular, has been driven in part by their lower risk for extrapyramidal symptoms (EPS) compared with first-generation antipsychotics (FGAs).¹ However, a growing body of data indicates that all antipsychotics have a range of adverse effects in older patients. This focus is critical in light of demographic trends—in the next 10 to 15 years, the population age >60 will grow 3.5 times more rapidly than the general population.²

In this context, psychiatrists need information on the relative risks of antipsychotics for older patients. This 3-part series summarizes findings and recommendations on safety and tolerability when prescribing antipsychotics in older individuals with chronic psychotic disorders, such as schizophrenia, bipolar disorder, depression, and dementia. This review aims to:

- briefly summarize the major studies and analyses relevant to older patients with these diagnoses
- provide a summative opinion on safety and tolerability issues in these older adults
- highlight the gaps in the evidence base and areas that need additional research.

Part 1 focuses on older adults with schizophrenia or bipolar disorder. Subsequent articles will focus on prescribing antipsychotics to older adults with depression and those with dementia.

continued



Antipsychotics in geriatric patients

Clinical Point

Studies suggest that older patients develop extrapyramidal symptoms with lower antipsychotic doses despite lower receptor occupancy



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Table 1

Common symptoms to target in older adults with schizophrenia

Positive symptoms may decline over time:

- hallucinations
- delusions
- hyperactivity

Negative symptoms may worsen over time:

- lack of motivation
- social withdrawal
- cognitive deterioration

Source: References 5,6

Schizophrenia

Summary of benefits, place in treatment armamentarium. Individuals with schizophrenia have a shorter life expectancy than that of the general population mostly as a result of suicide and comorbid physical illnesses,³ but the number of patients with schizophrenia age >55 will double over the next 2 decades.⁴ With aging, both positive and negative symptoms may be a focus of treatment (*Table 1*).^{5,6} Antipsychotics are a first-line treatment for older patients with schizophrenia with few medication alternatives.⁷ Safety risks associated with antipsychotics in older people span a broad spectrum (*Table 2, page 23*).⁸

Clinical trials. Few studies have evaluated treatment of older adults with schizophrenia.⁷⁻¹³ Two Cochrane reviews found only a handful of randomized controlled trials (RCTs).^{10,11} The largest RCT was an 8-week prospective, multisite RCT of olanzapine vs risperidone in 175 older adults (age ≥60 years; mean age, 71 years) with schizophrenia.⁵ Before enrollment, just over one-half (53%) had been treated with FGAs. Both risperidone and olanzapine were flexibly dosed, with a target dose of 3 mg/d for risperidone and 20 mg/d for olanzapine. Median daily doses were 2 mg/d for risperidone and 10 mg/d for olanzapine. Both treatments were associated with symptom improvement, but there was no difference between groups. Approximately 70% of patients in each treatment arm experienced adverse events. The most common adverse

effects (similar across groups) were somnolence, insomnia, dizziness, agitation, constipation, headache, and diarrhea. Rates of EPS were lower with both risperidone (9.2% EPS-related adverse effects) and olanzapine (15.9% EPS-related adverse effects) vs patients taking FGAs prior to starting the RCT. Drop-out rates were similar (risperidone, 19.3%; olanzapine, 27.6%). There was greater weight gain with olanzapine vs risperidone ($P = .04$).⁵

A 6-week prospective RCT evaluated paliperidone extended-release vs placebo in 114 older adults (age ≥65 years; mean age, 70 years) with schizophrenia.¹⁴ There was an optional 24-week extension of open-label treatment with paliperidone. Mean daily dose of paliperidone was 8.4 mg. Efficacy measures did not show consistent statistically significant differences between treatment groups. Discontinuation rates were similar between paliperidone (7%) vs placebo (8%). Serious adverse events occurred in 3% of paliperidone-treated vs 8% of placebo-treated patients. Elevated prolactin levels occurred in one-half of paliperidone-treated patients. There were no prolactin or glucose treatment-related adverse events or significant mean changes in body weight for either paliperidone-treated or placebo-treated patients. Safety findings in the 24-week, open-label extension group were consistent with the RCT results.

Howanitz et al¹⁵ conducted a 12-week, prospective RCT that compared clozapine (mean dose, 300 mg/d) with chlorpromazine (mean dose, 600 mg/d) in 42 older adults (mean age, 67 years) with schizophrenia. Drop-out rate prior to 5 weeks was 19% and similar between groups. Common adverse effects included sialorrhea, hematologic abnormalities, sedation, tachycardia, EPS, and weight gain. Although both drugs were effective, more patients taking clozapine had tachycardia and weight gain, while more chlorpromazine patients reported sedation.

There have been other, less rigorous studies.^{7,8} Most of these studies evaluated risperidone and olanzapine, and most were conducted in “younger” geriatric patients (age <75 years). Although patients who participate in clinical trials may be healthier

than “typical” patients, adverse effects such as EPS, sedation, and weight gain were still relatively common in these studies.

Other clinical data. A major consideration in treating older adults with schizophrenia is balancing the need to administer an antipsychotic dose high enough to alleviate psychotic symptoms while minimizing dose-dependent adverse effects. There is a U-shaped relationship between age and vulnerability to antipsychotic adverse effects,^{16,17} wherein adverse effects are highest at younger and older ages. Evidence supports using the lowest effective antipsychotic dose for geriatric patients with schizophrenia. Positive emission tomography (PET) studies suggest that older patients develop EPS with lower doses despite lower receptor occupancy.^{17,18} A recent study of 35 older patients (mean age, 60.1 years) with schizophrenia obtained PET, clinical measures, and blood pharmacokinetic measures before and after reduction of risperidone or olanzapine doses.¹⁸ A ≥40% reduction in dose was associated with reduced adverse effects, particularly EPS and elevation of prolactin levels. Moreover, the therapeutic window of striatal D2/D3 receptor occupancy appeared to be 50% to 60% in these older patients, compared with 65% to 80% in younger patients.

Long-term risks of antipsychotic treatment across the lifespan are less clear, with evidence suggesting both lower and higher mortality risk.^{19,20} It is difficult to fully disentangle the long-term risks of antipsychotics from the cumulative effects of lifestyle and comorbidity among individuals who have lived with schizophrenia for decades. Large naturalistic studies that include substantial numbers of older people with schizophrenia might be a way to elicit more information on long-term safety. The Schizophrenia Outpatient Health Outcome (SOHO) study was a large naturalistic trial that recruited >10,000 individuals with schizophrenia in 10 European countries.²¹ Although the SOHO study found differences between antipsychotics and adverse effects, such as EPS, weight gain, and sexual dysfunction, because the mean age of these patients was approximately 40 years and the follow-up

Table 2

Antipsychotic adverse effects that are more common in older patients^a

Cardiovascular changes (prolonged QTc, arrhythmia, stroke, sudden death)
Hematologic changes (bleeding alteration, reduced white blood counts and platelets, altered bone metabolism)
Metabolic/endocrine changes (metabolic syndrome, type 2 diabetes mellitus, weight gain)
Electrolyte imbalance (hyponatremia)
Extrapyramidal symptoms and tardive dyskinesia
Adverse effects that may be related to peripheral and central anticholinergic effects (constipation, urinary retention, cognitive dysfunction, delirium)
Adverse effects that may be related to antiadrenergic effects (postural hypotension, falls and fractures)
Adverse effects that may be related to antihistaminic effects (sedation, dry mouth, pneumonia)
Drug–drug interactions due to medical comorbidity and co-prescribed somatic therapies for medical conditions
Generally, medical comorbidity becomes more prominent and antipsychotics need to be co-prescribed carefully to avoid interactions with other medications for medical conditions
^a Some adverse effects and complications may be related to multiple drug-related factors. For example, weight gain could be related to both direct metabolic effects as well as decreased physical activity seen in a patient with drug-induced sedation
Source: Reference 8

period was only 3 years, it is difficult to draw conclusions that could be relevant to older individuals who have had schizophrenia for decades.

Bipolar Disorder

Summary of benefits, place in treatment armamentarium. Up to 25% of bipolar patients are elderly,²² and that number is projected to increase over the next decade.²³ Clinical considerations in older adults with bipolar disorder include medical comorbidity, depression burden, and possible cognitive decline (*Table 3, page 24*).^{24–27} Along with lithium and mood stabilizers, antipsychotics are a first-line treatment for

Clinical Point

A ≥40% reduction in antipsychotic dose was associated with reduced adverse effects, particularly EPS and elevations of prolactin levels



Antipsychotics in geriatric patients

Clinical Point

In older adults with bipolar disorder, consider medical comorbidity, depression burden, and possible cognitive decline

Table 3

Clinical considerations in older adults with bipolar disorder

Bipolar manic symptoms may be reduced or attenuated

Bipolar depressive symptoms may be more prominent and exert longer-term impact on functioning

Cognitive deterioration may occur over time

Medical comorbidity is extensive, with 3 to 6 chronic medical conditions being the norm

Source: References 24-27

bipolar disorder.²⁸⁻³⁰ Most FDA-approved antipsychotics for bipolar disorder are SGAs for bipolar mania. However, olanzapine-fluoxetine combination, quetiapine, and lurasidone are approved for bipolar depression. Aripiprazole, olanzapine, quetiapine, long-acting injectable risperidone, and oral ziprasidone are FDA-approved for longer-term use in adults with bipolar disorder. There are no head-to-head trials of antipsychotics for older persons with bipolar disorder.

Clinical trials: Bipolar depression.

A post hoc, secondary analysis of two 8-week, double-blind, randomized, placebo-controlled studies in bipolar depression compared 2 dosages of quetiapine (300 mg/d and 600 mg/d) with placebo in mixed-age patients.³¹ In a subgroup of 72 patients, ages 55 to 65, remission occurred more often with quetiapine than with placebo. Study discontinuation rates were similar between older people and younger people (age <55 years): quetiapine, 300 mg/d, 29.2%; quetiapine, 600 mg/d, 48.1%; and placebo, 29.6% in older adults, compared with 37.1%, 45.8%, and 38.1%, respectively, in younger adults. In all patients, the most common reason for discontinuation was adverse events with quetiapine and lack of efficacy for placebo. Adverse event rates were similar in older and younger adults. Dry mouth and dizziness were more common in older adults. Proportions of adults experiencing clinically significant weight gain ($\geq 7\%$ of body

weight) were 5.3%, 8.3%, and 0% in older adults receiving quetiapine, 300 mg/d, quetiapine, 600 mg/d, and placebo, respectively, compared with 7.2%, 10.1%, and 2.6% in younger adults. EPS and treatment-emergent mania were minimal.

A secondary analysis of mixed-age, RCTs examined response in older adults (age ≥ 55 years) with bipolar I depression who received lurasidone as monotherapy or adjunctive therapy.³² In the monotherapy study, these patients were randomized to 6 weeks of lurasidone 20 to 60 mg/d, lurasidone 80 to 120 mg/d, or placebo. In the adjunctive therapy study, they were randomized to lurasidone 20 to 120 mg/d or placebo with either lithium or valproate. There were 83 older adults (17.1% of the sample) in the monotherapy study and 53 (15.6%) in the adjunctive therapy study. Mean improvement in depression was significantly higher for both doses of lurasidone monotherapy than placebo. Adjunctive lurasidone was not associated with statistically significant improvement vs placebo. The most frequent adverse events in older patients on lurasidone monotherapy 20 to 60 mg/d or 80 to 120 mg/d were nausea (18.5% and 9.7%, respectively) and somnolence (11.1% and 0%, respectively). Akathisia (9.7%) and insomnia (9.7%) were the most common adverse events in the group receiving 80 to 120 mg/d, with the rate of akathisia exhibiting a dose-related increase. Weight change with lurasidone was similar to placebo, and there were no clinically meaningful group changes in vital signs, electrocardiography, or laboratory parameters.

A small (N = 20) open study found improvement in older adults with bipolar depression with aripiprazole (mean dose, 10.3 mg/d).³³ Adverse effects included restlessness and weight gain (n = 3, 9% each), sedation (n = 2, 10%), and drooling and diarrhea/loose stools (n = 1, 5% each). In another small study (N = 15) using asenapine (mean dose, 11.2 mg/d) in mainly older bipolar patients with depression, the most common adverse effects were gastrointestinal (GI) discomfort (n = 5, 33%) and restlessness, tremors, cognitive difficulties, and sluggishness (n = 2, 13% each).³⁴

Table 4

Antipsychotics for older patients with schizophrenia or bipolar disorder: Take-home points

Demographic data suggest the number of older adults with mental illness is increasing

Antipsychotics are extensively used in older patients for various psychiatric conditions

The evidence base to inform treatment of individuals with schizophrenia or bipolar disorder is limited. A major challenge is that there is a paucity of published randomized controlled trials or prospective naturalistic studies specific to older patients prescribed antipsychotics. Pharmacotherapy evidence is not keeping up with demographic trends

The evidence base is fairly solid on several key points:

- Second-generation antipsychotics (SGAs) are preferred treatment over first-generation antipsychotics in older patients because they are less likely to cause extrapyramidal symptoms and other neurologic adverse effects
- SGAs dosed appropriately appear to be relatively safe and well-tolerated for older patients with schizophrenia or bipolar disorder
- Older adults are more likely to experience adverse effects from medications than younger individuals

Additional research is needed to provide detailed and conclusive information regarding relative risks and burdens of using antipsychotics in geriatric patients

Clinical trials: Bipolar mania. Researchers conducted a pooled analysis of two 12-week randomized trials comparing quetiapine with placebo in a mixed-age sample with bipolar mania.³⁵ In a subgroup of 59 older patients (mean age, 62.9 years), manic symptoms improved significantly more with quetiapine (modal dose, 550 mg/d) than with placebo. Adverse effects reported by >10% of older patients were dry mouth, somnolence, postural hypotension, insomnia, weight gain, and dizziness. Insomnia was reported by >10% of patients receiving placebo.

In a case series of 11 elderly patients with mania receiving asenapine, Baruch et al³⁶ reported a 63% remission rate. One patient discontinued the study because of a new rash, 1 discontinued after developing peripheral edema, and 3 patients reported mild sedation.

Beyer et al³⁷ reported on a post hoc analysis of 94 older adults (mean age, 57.1 years; range, 50.1 to 74.8 years) with acute bipolar mania receiving olanzapine (n = 47), divalproex (n = 31), or placebo (n = 16) in a pooled olanzapine clinical trials database. Patients receiving olanzapine or divalproex had improvement in mania; those receiving placebo did not improve. Safety findings were comparable with reports in younger patients with mania.

Other clinical data. Adverse effects found in mixed-age samples using secondary analyses of clinical trials need to be interpreted with caution because these types of studies usually exclude individuals with significant medical comorbidity. Medical burden, cognitive impairment, or concomitant medications generally necessitate slower drug titration and lower total daily dosing. For example, a secondary analysis of the U.S. National Institute of Health-funded Systematic Treatment Enhancement Program for Bipolar Disorder study, which had broader inclusion criteria than most clinical trials, reported that, although recovery rates in older adults with bipolar disorder were fairly good (78.5%), lower doses of risperidone were used in older vs younger patients.³⁸

Clinical considerations

Interpretation of the relative risks of antipsychotics in older people must be tempered by the caveat that there is limited high-quality data (*Table 4*). Antipsychotics are the first-line therapy for older patients with schizophrenia, although their use is supported by a small number of prospective RCTs. SGAs are preferred because of their lower propensity to cause EPS and other

Clinical Point

Medical burden and other factors generally necessitate slower drug titration and lower total daily dosing in older patients



Antipsychotics in geriatric patients

Clinical Point

Be vigilant in monitoring for adverse effects that are more common in older adults, such as tardive dyskinesia

Related Resources

- Desai Ak, Seraji M, Redden M, et al. Schizophrenia in older adults. *Current Psychiatry*. 2010;9(9):22-28,A.
- Gareri P, Segura-García C, Manfredi VG, et al. Use of atypical antipsychotics in the elderly: a clinical review. *Clin Interv Aging*. 2014;9:1363-1373.

Drug Brand Names

Aripiprazole • Abilify, Abilify Maintena	Olanzapine-Fluoxetine • Symbyax
Asenapine • Saphris, Sycrest	Paliperidone extended-release • Invega
Chlorpromazine • Ormazine, Thorazine	Quetiapine • Seroquel
Clozapine • Clozaril, FazaClo	Risperidone • Risperdal, Risperdal Consta
Divalproex • Depakote	Valproate • Depakene
Lithium • Eskalith, Lithobid	Ziprasidone • Geodon
Lurasidone • Latuda	
Olanzapine • Zyprexa, Zyprexa Relprevv	

motor adverse effects. Older persons with schizophrenia have an EPS threshold lower than younger patients and determining the lowest effective dosage may minimize EPS and cognitive adverse effects. As individuals with long-standing schizophrenia get older, their antipsychotic dosages may need to be reduced, and clinicians need to monitor for adverse effects that are more common among older people, such as tardive dyskinesia and metabolic abnormalities. In healthy, “younger” geriatric patients, monitoring for adverse effects may be similar to monitoring of younger patients. Patients who are older or frail may need more frequent assessment.

Like older adults with schizophrenia, geriatric patients with bipolar disorder have reduced drug tolerability and experience more adverse effects than younger patients. There are no prospective controlled studies that evaluated using antipsychotics in older patients with bipolar disorder. In older bipolar patients, the most

problematic adverse effects of antipsychotics are akathisia, parkinsonism, other EPS, sedation and dizziness (which may increase fall risk), and GI discomfort. A key tolerability and safety consideration when treating older adults with bipolar disorder is the role of antipsychotics in relation to the use of lithium and mood stabilizers. Some studies have suggested that lithium has neuroprotective effects when used long-term; however, at least 1 report suggested that long-term antipsychotic treatment may be associated with neurodegeneration.³⁹

The literature does not provide strong evidence on the many clinical variations that we see in routine practice settings, such as combinations of drug treatments or drugs prescribed to patients with specific comorbid conditions. There is a need for large cohort studies that monitor treatment course, medical comorbidity, and prognosis. Additionally, well-designed clinical trials such as the DART-AD, which investigated longer-term trajectories of people with dementia taking antipsychotics, should serve as a model for the type of research that is needed to better understand outcome variability among older people with chronic psychotic or bipolar disorders.⁴⁰

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Bottom Line

There is limited data available on the safety and efficacy of antipsychotics in geriatric patients with schizophrenia or bipolar disorder. When dosed appropriately, second-generation antipsychotics are preferred over first-generation antipsychotics in this population because they are less likely to cause extrapyramidal symptoms and other neurologic adverse effects.



Antipsychotics in geriatric patients

Clinical Point

In older patients with bipolar disorder, consider the role of antipsychotics in relation to the use of lithium and mood stabilizers

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