

Use of Atypical Antipsychotic Drugs in Patients with Dementia

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Increasingly, atypical antipsychotic drugs are prescribed for elderly patients with symptoms of psychosis and behavioral disturbances. These symptoms often occur in patients with Alzheimer's disease, other dementias, or Parkinson's disease. As the average age of Americans increases, the prevalence of Alzheimer's disease and Parkinson's disease will rise accordingly. Although nonpharmacologic treatments for behavioral disturbances should be tried first, medications often are needed to enable the patient to be adequately cared for. Current guidelines recommend using risperidone and olanzapine to treat psychosis in patients with Alzheimer's dementia. Quetiapine and clozapine are recommended for treatment of psychosis in patients with Parkinson's disease. Additional research is needed for a recently approved agent, ziprasidone. To minimize side effects, these medications should be started at low dosages that are increased incrementally. Drug interactions, especially those involving the cytochrome P450 system, must be considered. Clozapine's potentially lethal side effects limit its use in the primary care setting. Informed use of atypical antipsychotic drugs allows family physicians to greatly improve quality of life in elderly patients with dementia and behavior disturbances. (Am Fam Physician 2003;67:2335-40. Copyright© 2003 American Academy of Family Physicians)

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Most family physicians are comfortable prescribing antidepressants, but antipsychotic medications are less commonly prescribed and therefore less familiar. Antipsychotic drugs effectively treat psychosis caused by a variety of conditions (Table 1). Psychotic symptoms are classified as either positive or negative. Positive symptoms include hallucinations, delusions, thought disorders (manifested by marked incoherence, derailment, tangentiality), and bizarre or disorganized behavior. Negative symptoms include anhedonia, flattened affect, apathy, and social withdrawal.¹

Psychotic symptoms in elderly patients always should be investigated thoroughly, and underlying medical conditions should be identified and treated. Although a family physician is less likely to manage schizophrenia in elderly patients, it is quite common for family physicians to treat patients who have Alzheimer's disease and Parkinson's disease. These patients frequently have psychotic symptoms that are treated without a specialist's aid.

Typical antipsychotic drugs, such as haloperidol (Haldol), traditionally have been used to control psychotic and behavior disturbances in elderly patients, but these drugs have troubling side effects. Extrapyramidal symptoms can cause stiffness, immobility, and falls and are associated with significant mor-

TABLE 1
Some Causes of Psychotic Symptoms in Elderly Patients

Primary psychiatric conditions
Schizophrenia
Mood disorders with psychotic features
Substance abuse or intoxication
Delirium*
Dementia*
Intracranial lesions
Tumor
Stroke
Subdural hematoma

*—Syndromes with multiple potential etiologies.

See page 2241 for definitions of strength-of-evidence levels.

bidity. The newer atypical antipsychotic drugs offer distinct advantages over older agents, including decreased extrapyramidal symptoms and improved efficacy in treatment of the negative symptoms of psychosis. Family physicians should become familiar with the use of atypical antipsychotic drugs in elderly patients (Table 2).

Atypical antipsychotic drugs are especially useful in treating symptoms associated with common neuropsychiatric disorders, such as Alzheimer's disease and Parkinson's disease.²⁻⁴ As the number of elderly people in the United

States increases, the use of atypical antipsychotic drugs is expected to increase substantially. The National Institutes of Health estimates that there will be 8.5 million Americans with Alzheimer's disease by the year 2030.⁵ Psychotic symptoms are present in at least 25 percent of mildly demented patients with Alzheimer's disease and in 50 percent of patients with advanced Alzheimer's disease.⁶ Among persons older than 65 years, the incidence of Parkinson's disease is 2 percent.⁷ Hallucinations occur in up to 20 percent of patients with Parkinson's disease; delusions,

TABLE 2
Summary of Atypical Antipsychotic Drugs Used in Elderly Patients

Drug	Evidence for use in patients with Alzheimer's disease?	Evidence for use in patients with Parkinson's disease?	Dosage in the elderly	Common or major side effects*	Cytochrome P450 system	Cost per month†
Clozapine (Clozaril)	Limited	Yes	6.5 to 75 mg per day	Agranulocytosis, hypotension, seizures, sialorrhea, weight gain, tachycardia, hyperthermia, hyperglycemia	1A2‡ 2D6§	\$11 to \$132
Olanzapine (Zyprexa)	Yes	No	1.25 to 5 mg per day	Weight gain, hypotension, seizures, hyperglycemia	1A2‡	\$78 to \$184
Quetiapine (Seroquel)	No	Yes	12.5 to 200 mg per day	Hypotension, headache, weight gain, cataract formation	3A4	\$22 to \$151
Risperidone (Risperdal)	Yes	No	0.25 to 3 mg per day	Extrapyramidal symptoms, hypotension, hyperprolactinemia, insomnia, weight gain	2D6§	\$84 to \$164
Ziprasidone (Geodon)	No	No	Not studied	QT prolongation, rash, hypertension	3A4	N/A

N/A = not available.

*—All of these medications can cause sedation. All atypical antipsychotic agents can cause hyperglycemia (contributing to type II diabetes mellitus), although this most often occurs with olanzapine and clozapine.

†—Estimated cost to the pharmacist based on average wholesale prices in Red book. Montvale, N.J.: Medical Economic Data, 2002. Cost to the patient will be higher, depending on prescription-filling fee.

‡—1A2 inhibitors: cimetidine (Tagamet), fluoroquinolones, fluvoxamine (Luvox); can increase effects of the antipsychotic agent.

§—2D6 inhibitors: celecoxib (Celebrex), amiodarone (Cordarone), cimetidine, paroxetine (Paxil), fluoxetine (Prozac); can increase effects of the antipsychotic agent.

||—3A4 inhibitors: ciprofloxacin (Cipro), fluoxetine, grapefruit juice, erythromycin, ketoconazole (Nizoral), diltiazem (Cardizem); can increase effects of the antipsychotic agent. 3A4 enhancer: phenytoin (Dilantin); can enhance metabolism of clozapine and quetiapine.

paranoia, and subcortical dementia also may occur.^{8,9}

Treatment of Behavior Disturbances

Initial interventions for behavior disturbances should include cognitive, environmental, and social techniques. Many demented patients with behavior disturbances will not need psychotropic medication but can be managed successfully with nonpharmacologic techniques, such as the use of familiar objects, maintenance of sleep-wake cycles, redirection, and frequent reorienting (verbally or by posting a calendar in their room).

There are many differences of opinion about when medications are indicated. There is even conflicting evidence about the efficacy of medications in treating behavior symptoms in dementia.^{10,11} Therefore, decisions to use these medications should be made on a case-by-case basis. Most guidelines call for the use of medications only when other methods have failed. The Health Care Financing Administration has produced regulations governing the use of psychotropic medications in nursing homes. Several authors have adapted these regulations into clinically useful guidelines (*Table 3*).^{12,13}

Typical Antipsychotic Agents

Psychotic symptoms traditionally have been treated with so-called “typical” antipsychotic drugs—older agents such as haloperidol and thioridazine (Mellaril). These medications have a variety of pharmacologic actions. Their ability to block the dopamine (D₂) receptor in the mesolimbic system reduces positive symptoms of psychosis. The D₂ blockade in the nigrostriatal pathway causes extrapyramidal symptoms, which include drug-induced parkinsonism, akathisia, acute dystonia, and tardive dyskinesia. The D₂-receptor blockade in the tuberoinfundibular pathway increases serum levels of prolactin, which may present clinically as breast tenderness, galactorrhea, or erectile dysfunction.¹ Younger patients may present with amenorrhea.

The pharmacodynamic action of atypical antipsychotic drugs is attributed to their action on both the serotonergic and dopaminergic systems.

TABLE 3
Appropriate Use of Antipsychotic Agents in the Elderly*

Use only one antipsychotic agent at a time.

Use an antipsychotic drug only if the clinical record documents one of the following conditions:

Schizophrenia	Schizo-affective disorder
Delusional disorder	Psychotic mood disorders
Acute psychotic episodes	Brief reactive psychosis
Schizophreniform disorder	Atypical psychosis
Tourette’s syndrome	Huntington’s disease

Organic mental syndromes associated with psychotic or agitated features as defined by at least one of the following:

- Specific behaviors (biting, kicking, scratching), quantitatively documented by the facility, that cause the resident to present a danger to himself/herself or others (including staff) or that interfere with the staff’s ability to provide care
- Continuous crying out, screaming, yelling, or pacing, if these behaviors impair functional capacity and if they are quantitatively documented by the facility
- Psychotic symptoms (hallucinations, paranoia, delusions) not exhibited as specific behaviors in schizophrenia and schizo-affective disorder, if these behaviors impair functional capacity

Gradual dosage reduction should be attempted every six months after therapy begins. Gradual dosage reductions should be targeted to the lowest possible dosage to control symptoms.

Use of a listed antipsychotic drug should be avoided if one or more of the following behaviors is the only indication for its use:

Wandering	Poor self-care
Restlessness	Impaired memory
Anxiety	Depression
Insomnia	Unsociability
Indifference to surroundings	Fidgeting
Nervousness	Uncooperativeness
Unspecified agitation	

*—Recommendations are based on standards from the Health Care Financing Administration.

Adapted with permission from Ruby CM, Kennedy DH. Psychopharmacologic medication use in nursing home care: indicators for surveyor assessment of the performance of drug regimen reviews, recommendation for monitoring, and non-pharmacologic alternatives. *Clin Fam Pract* 2001;3:577-98, with information from reference 13.

Atypical Antipsychotic Agents

The pharmacodynamic action of atypical antipsychotic drugs is attributed to their action on both the serotonergic and dopaminergic systems. Some experts argue that this combination of relative effects on dopamine and serotonin allows atypical antipsychotic drugs to treat both positive and negative symptoms of psychosis while producing fewer extrapyramidal symptoms and decreasing iatrogenic hyperprolactinemia.¹⁴

There is growing concern over recent reports of hyperglycemia in patients who are taking certain atypical antipsychotic drugs. The increased rate of hyperglycemia appears to be independent of weight gain. These findings have led some investigators to recommend screening for diabetes twice a year in patients who are taking atypical antipsychotic drugs.¹⁵

RISPERIDONE

Risperidone (Risperdal) usage in Alzheimer's disease and Parkinson's disease has mixed results. Significant evidence demonstrates the efficacy of risperidone in the treatment of psychotic and behavior symptoms in patients with dementia.^{10,16,17} [References 10 and 17—Evidence level A, randomized controlled trials (RCTs)] However, risperidone exacerbates

movement disorders in patients with Parkinson's disease and has been shown to be less effective than clozapine (Clozaril) in controlling psychosis in these patients.¹⁸⁻²⁰

Initial dosages of 0.25 mg per day are titrated slowly upward to achieve the desired effect. In two studies^{10,17} documenting the efficacy of risperidone in patients with dementia, the mean dosages were 1.1 mg per day and 1.2 mg per day. Risperidone causes extrapyramidal symptoms in a dosage-dependent manner, so the lowest effective dosage is used.

Significant side effects of risperidone include insomnia, hypotension, weight gain, and extrapyramidal symptoms. Extrapyramidal symptoms are more likely when the dosage is more than 6 mg per day.²¹ Risperidone is metabolized by the cytochrome P450 2D6 system. Any medication that affects this enzyme (e.g., celecoxib [Celebrex], amiodarone [Coradarone], cimetidine [Tagamet], fluoxetine [Prozac], paroxetine [Paxil]) can alter the efficacy of risperidone. Risperidone causes a significant elevation in prolactin levels. Caution should be used when prescribing risperidone with other medications that cause hypotension.

OLANZAPINE

Studies indicate that olanzapine (Zyprexa) is an effective treatment for psychotic and behavior symptoms in patients with Alzheimer's disease.^{22,23} [Reference 22—Evidence level A, RCT] However, in patients with Parkinson's disease, olanzapine was found to increase motor symptoms and to be less effective than clozapine. Therefore, current recommendations discourage the use of olanzapine in patients with Parkinson's disease.²⁴ [Evidence level B, uncontrolled study]

In patients with Alzheimer's disease and psychotic symptoms, dosages should start at 1.25 to 2.5 mg per day and increase to 5 mg per day, if necessary. Surprisingly, dosages of 10 or 15 mg per day are less effective than dosages of 5 mg per day.²²⁻²⁶ Common side effects of olanzapine include sedation and weight gain. Special considerations in elderly

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patients include the risk of orthostatic hypotension and seizures. In pre-marketing testing, olanzapine was associated with a 0.9 percent rate of seizures. Seizures occurred in patients with confounding factors; consequently, this medication should be used with caution in patients who have a lowered seizure threshold.²¹ Olanzapine is metabolized by the cytochrome P450 1A2 system, as well as multiple other hepatic pathways, and therefore has a low potential for drug-drug interactions.

QUETIAPINE

Quetiapine (Seroquel) has shown promise in the treatment of psychosis in elderly patients with Alzheimer's disease and Parkinson's disease. It improves psychosis in patients with Parkinson's disease without exacerbating movement disorders. This feature has led some experts to recommend it as the first-line agent for treatment of psychosis in patients with Parkinson's disease.^{27,28} [Reference 28—Evidence level B, uncontrolled study] It has been shown to be safe in patients with Alzheimer's disease, but more controlled trials are needed before its use in these patients can be endorsed.²⁹

Quetiapine should be initiated at a dosage of 12.5 mg at bedtime and titrated every three to five days until the desired effect is achieved or side effects emerge. Common side effects include sedation, headache, and orthostatic hypotension. Cataract formation was noticed in pre-marketing studies, but a causal relationship has not been found. Screening for cataract formation is recommended at the initiation of therapy and at six-month intervals thereafter.²¹ Quetiapine is metabolized by the cytochrome P450 3A4 system. Serum levels of quetiapine can be affected by inducers or inhibitors of this enzyme system (e.g., ketoconazole [Nizoral], erythromycin, diltiazem [Cardizem], fluoxetine, ciprofloxacin [Cipro], grapefruit juice, and phenytoin [Dilantin]).²¹

ZIPRASIDONE

Because ziprasidone (Geodon) was recently released, clinical data are lacking to support

its use in patients with either Parkinson's disease or Alzheimer's disease. Side effects of ziprasidone include rash, hypertension, and (rarely) non-dose-dependent QT-interval prolongation. Ziprasidone should be avoided in patients at risk for significant electrolyte abnormalities and in patients with histories of significant cardiovascular illness, recent acute myocardial infarction, uncompensated heart failure, and cardiac arrhythmia. Ziprasidone is metabolized by the cytochrome P450 3A4 system.²¹

CLOZAPINE

Research on clozapine in the geriatric population has had mixed results. Clozapine is highly effective in treating psychosis in patients with Parkinson's disease.³⁰ [Evidence Level A, RCT] The American Academy of Neurology states that clozapine appears to be the most effective agent in the treatment of drug-induced psychosis in patients with Parkinson's disease.^{18,30} Clozapine has shown some efficacy in controlling psychosis and behavior disturbances in patients with Alzheimer's disease.^{16,31} Initial dosages can start as low as 6.5 mg per day and are titrated upward.

Clozapine is well known for its side effects, which include agranulocytosis (with a fatality rate as high as 30 percent), sedation, seizures, sialorrhea, hypotension, weight gain, tachycardia, and hyperthermia.²¹ A complete blood count must be checked frequently in patients taking this medication. Because of its serious and potentially lethal side effects, clozapine generally is used only after other options have failed. Clozapine is metabolized by the cytochrome P450 1A2 and 2D6 systems.

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