Notice of Correction—In the original publication, the date of the grant was omitted. The last sentence of the first paragraph (page 131, left column) has been corrected to read: "Support for this project was provided by an educational grant from Bristol-Myers Squibb, Inc., awarded in November 2005."

A Roadmap to Key Pharmacologic Principles in Using Antipsychotics in the Treatment of Older Patients

The case examples and discussions in this ACADEMIC HIGHLIGHTS section were developed by George S. Alexopoulos, M.D., a member of the Roadmap Editorial Board, to illustrate clinical issues in the use of antipsychotics in the treatment of older patients. The recommendations in this article are based in part on those previously published in a supplement on antipsychotic use by Peter J. Weiden, M.D.; Sheldon H. Preskorn, M.D.; Peter A. Fahnestock, M.D.; Daniel Carpenter, Ph.D.; Ruth Ross, M.A.; and John P. Docherty, M.D., titled Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap.[1] *Dr. Alexopoulos acknowledges the authors of that supplement and the other members of the Roadmap Editorial Board (Shitij Kapur, M.D., Ph.D., F.R.C.P.C.; David C. Mamo, M.D., M.Sc., F.R.C.P.C.; Stephen R. Marder, M.D.; Joseph P. McEvoy, M.D.; John W. Newcomer, M.D.; and Gary S. Sachs, M.D.), the experts who completed the survey, and Paola Vega of Expert Knowledge Systems for their invaluable help. Support for this project was provided by an educational grant from Bristol-Myers Squibb, Inc., awarded in November 2005.*

Disclaimer: The authors note that any set of published recommendations can provide only general suggestions for clinical practice and practitioners must use their own clinical judgment in treating and addressing the needs of each individual patient, taking into account that patient's unique clinical situation. There is no representation of the appropriateness or validity of the Roadmap recommendations for any given patient. The developers of the Roadmap recommendations disclaim all liability and cannot be held responsible for any problems that may arise from their use.

The faculty for this CME activity, the CME Institute staff, and Comprehensive NeuroScience, Inc., staff were asked to complete a statement regarding all relevant financial relationships between themselves or their spouse/partner and any commercial interest. The CME Institute has resolved any conflicts of interest that were identified. No member of either Comprehensive NeuroScience, Inc., or the CME Institute reported any relevant personal financial relationships. The faculty financial disclosure is as follows: ***Dr. Alexopoulos*** *is a consultant for the Scientific Advisory Board of Forest, has received grant/research support from Cephalon and Forest, and is a member of the speakers/advisory boards for Forest, Eli Lilly, Bristol-Myers Squibb, Pfizer, and Janssen.*

The opinions expressed herein are those of the faculty and do not necessarily reflect the views of the CME provider and publisher, the joint sponsor, the American Society of Clinical Psychopharmacology, or the commercial supporter.

Antipsychotics are widely used to treat psychiatric disorders in older patients. While the growing number of second-generation antipsychotics (SGAs) has increased options for patients, it has also complicated clinical decision-making. Data from the American Psychiatric Association's (APA's) Practice Research Network indicated disproportionately high use of antipsychotics and benzodiazepine medications among older patients compared with those under age 65.[2] It also found higher rates of Axis III comorbidity (i.e., general medical conditions) among older patients receiving psychiatric care than among younger patients. A recent review of medication use in 1354 nursing home residents in Norway found potential medication problems in 76% of the patients, with psychoactive drugs accounting for 38% of the problems, antipsychotics the class most often involved, and use of multiple psychoactive drugs particularly problematic.[3] High rates of adverse drug reactions are reported in older patients in long-term care settings, with use of antipsychotics an independent risk factor for such events.[3,4] This problem is compounded because many older patients are treated by primary care physicians or internists, some of whom may not be completely familiar with use of antipsychotics. Data from controlled trials in older patients are also limited due to difficulties conducting studies in this population. A better understanding of psychopharmacologic principles involved in using antipsychotics has the potential to improve use of these agents in older patients. This article summarizes recommendations from the supplement, *Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap*[1] and illustrates how to apply those recommendations in a series of cases as a guide for clinicians who use antipsychotics in older patients.

The President's New Freedom Commission on Mental Health[5] stressed the importance of incorporating the latest scientific information into mainstream health care as rapidly as possible. The Roadmap therefore drew on clinical trial data, information on antipsychotic pharmacology, practice guidelines,[6–11] consensus statements,[12] and expert opinion to develop recommendations to help clinicians make informed decisions in selecting, dosing, and switching antipsychotic medications. Expert opinion was sampled using an initial survey and roundtable meeting of 10 experts and a follow-up survey of 27 experts, who reached a high level of consensus on many key questions not adequately addressed by the literature. For a description of the survey methodology and respondents, see the Roadmap supplement.[1]

Pharmacologic Principles

The equation in Figure 1 shows the 3 major variables that determine a drug's effects in a specific patient.[13] The Roadmap survey asked the experts how the factors in this equation can help guide medication choices over and above data from clinical trials. Questions such as these are particularly pertinent for antipsychotics, which differ considerably in their pharmacologic properties. Such differences can be important in predicting side effects and avoiding withdrawal or additive effects when drugs are titrated, tapered, or combined. The following

Reprinted with correction to page 131.

Figure 1. Three Variables That Determine Response to Any Drug[a]

Clinical response = Affinity for the site of action (pharmacodynamics) × Drug concentration at site of action (pharmacokinetics) (ADME)
- Absorption
- Distribution
- Metabolism
- Elimination

× Underlying biology of patient (GADE)
- Genetics
- Age
- Disease
- Environment

[a]Reprinted with permission from Preskorn.[13]

Table 1. Binding Affinity of Selected Antipsychotics for Specific Neuroreceptors[a,b]

Antipsychotic	D_2	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	α_1	H_1	M_1
Aripiprazole	0.34[c]	1.7[c]	3.4[c]	15	57	61[c]	> 1000
Clozapine	126	875	16	16	7	6	1.9
Haloperidol	0.7	1100	45	> 10,000	6	440	> 1500
Olanzapine	11	> 10,000	4	23	19	7	1.9
Quetiapine	160	2800	295	1500	7	11	120
Risperidone	4	210	0.5	25	0.7	20	> 10,000
Ziprasidone	5	3	0.4	1	11	50	> 1000

[a]From Preskorn,[16] with permission, based on Richelson,[19] Abilify package insert,[20] Arnt and Skarsfeldt,[21] Bymaster et al.,[22] and Seeger et al.[23]
[b]Data represented as K_i (nM).
[c]Data with cloned human receptors.
Abbreviations: 5-HT = serotonin, α_1 = alpha-1 norepinephrine, D = dopamine, H_1 = histamine 1, M_1 = muscarinic acetylcholine-1.

Table 2. Common Adverse Effects Caused by Receptor Blockade[a]

Receptors	Effects
Histamine H_1	Sedation, weight gain, postural dizziness
α_1-Adrenergic	Hypotension
M_1	Deficits in memory and cognition, dry mouth, constipation, tachycardia, blurred vision, urinary retention
Dopamine D_2	Extrapyramidal side effects, prolactin elevation

[a]Based on Gardner et al.[18]
Abbreviations: α_1 = alpha-1 norepinephrine, M_1 = muscarinic acetylcholine-1.

sections briefly describe the variables in the equation as background for the case discussions that follow. For more detail, see the Roadmap supplement[1] and other publications on pharmacology of psychiatric drugs.[14–18]

Determinants of Clinical Response

Pharmacodynamics. A drug's effects are a function of the site(s) of action to which it binds, how many sites it occupies and for how long, and its actions at these site(s) (e.g., agonism, antagonism) (as well as actions of any active metabolites). Agonists act like the endogenous neurotransmitter, binding to and activating a receptor. Antagonists produce no activation and prevent the receptor from binding to other ligands. Drugs can also fall between these points (e.g., a partial agonist may produce some activation of a receptor, while preventing full activation). A drug can affect just 1 site of action (i.e., be selective) at clinically relevant concentrations or more than 1 site of action as a function of its relative binding affinity for more than 1 regulatory protein. (Binding affinity does not indicate the effect—e.g., agonism or antagonism—a drug has on its target; thus, a drug may bind tightly to its receptor without activating it.)

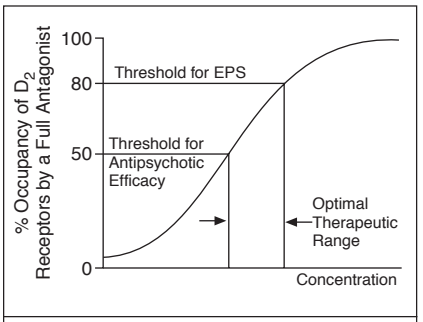
The relationship between receptor binding profiles and adverse effects is better understood than the effect of receptor binding profiles on efficacy. All currently available antipsychotics block dopamine-2 (D_2) receptors to some extent but vary in the degree to which they affect the D_2 receptor relative to other clinically meaningful receptors. These differences in receptor binding affinities (Table 1) explain some differences in the clinical profiles of these drugs, such as their propensity to cause extrapyramidal symptoms (EPS) (Table 2).[18]

The pharmacology and clinical profile of antipsychotics that affect multiple receptors change as the dose increases and the drug sequentially engages different target receptors in a dose-dependent, concentration-dependent manner.[16] For example, quetiapine binds most potently to the histamine-1 (H_1) and the alpha-1 norepinephrine (α_1) receptors and only affects other receptors as its dose and hence concentration increases. To achieve D_2 occupancy, the dose and hence concentration of quetiapine must typically be increased to a level 10 times higher than is needed to affect the H_1 and α_1 receptors.[1,18] Thus, while lower doses (e.g., 50 mg) may be effective for sedation, randomized controlled trials suggest that doses of 400 to 600 mg are usually needed for an antipsychotic effect.[24] Ziprasidone's affinity for the 5-HT_{2A} receptor is 10 times more potent than for the D_2 receptor, so that it blocks 5-HT_{2A} receptors at low doses (e.g., 20 mg) but has little effect on D_2 receptors until doses reach 120 to 160 mg/day.[1,23] Differences in relative engagement of serotonin and dopamine receptors may explain why early "activation" and insomnia sometimes seen with ziprasidone (thought to be mediated by serotonin mechanisms) are associated with lower doses and abate at higher doses (e.g., 120 mg/day) when that effect is mitigated by effects on D_2 receptors.[25] In contrast, early activation and insomnia sometimes seen with aripiprazole are believed to be associated with dopamine agonism and are more common at higher doses.[1,25] Since aripiprazole appears to have a flat dose-response curve between 15 and 30 mg/day, aiming for a target dose at the lower end of that range can help minimize problems with activation with this agent.[25]

Because of their effects on the D_2 receptor, antipsychotics can cause EPS. Generally, D_2 blockade greater than

Reprinted with correction to page 131.

Figure 2. Narrow Range Between Efficacy and Behavioral Toxicity With D_2 Receptor Antagonists[a,b]



[a]Reprinted with permission from Preskorn.[28]
[b]D_2 antagonism ≥ 50% appears needed for antipsychotic efficacy, while antagonism > 80% is associated with increased risk of acute extrapyramidal side effects (EPS).[26] This curve explains the narrow window between efficacy and EPS with full D_2 antagonists (note the curve would differ for partial D_2 agonists).

80% is associated with a markedly increased risk of acute EPS,[26,27] so that unopposed D_2 antagonism is associated with a relatively narrow window between efficacy and risk of acute EPS (Figure 2). It has been postulated that the newer antipsychotics have a lower risk of EPS because of the mediating effects of other receptors they affect. The new class of D_2 partial agonists has a lower risk of EPS because of agonist activity at the D_2 receptor; thus, aripiprazole has 30% of dopamine's intrinsic activity at the D_2 receptor and hence cannot exceed the equivalent of 70% blockade (antagonism) of D_2 receptors even if it occupies 100% of those receptors.[1,20] This is confirmed by studies showing that doses of aripiprazole that produce 95% occupancy of D_2 receptors in the striatum are not associated with increased risk of EPS.[20]

Pharmacokinetics refer to ways in which drugs enter and leave the body and the biological sites they affect. All antipsychotics cross the blood-brain barrier and find their way to the synapse, and are then cleared from the synapse and later from the body. Differences in how antipsychotics are metabolized are relevant to questions about long-acting antipsychotics, coprescribed medications, and how quickly to cross-taper drugs when switching antipsychotics.

Biological variability. There is significant variation in how the same medication at the same dose may affect different individuals. This article focuses on age as a source of biological variability. Other factors that can affect how medication acts include gender, comorbid medical conditions, other medications the person is taking, and individual genetic variability in receptor activity or metabolic pathways. Some variations in response cannot be predicted given our current level of knowledge (e.g., clinically important but currently unknown genetic differences), although tests for some variations in drug-metabolizing enzymes have become available.[29]

Treatment Issues in Older Patients

Before discussing specific cases, it is important to briefly review some issues that frequently arise in the treatment of older patients with serious mental illness.

Diagnostic Issues

In diagnosing primary psychotic disorders (e.g., schizophrenia, bipolar disorder with psychosis, delusional disorder, psychotic depression) in older patients, it is important to distinguish these conditions from delirium, psychosis induced by medications or medical illness, and dementia, which are common among older patients.[10]

Drug Metabolism and Dosing

Regarding antipsychotic use in older patients, the APA Practice Guideline for the Treatment of Patients With Schizophrenia recommends using a quarter to half of the usual starting dose for healthy younger adults.[6] Older patients may metabolize these drugs more slowly and be more sensitive to side effects, particularly sedation, anticholinergic effects, and postural hypotension. Not surprisingly, 85% of the Roadmap experts indicated they would use a lower target dose and a slower titration schedule in older patients, in keeping with the clinical adage to "start low and go slow" because of the increased sensitivity and slower metabolism common in geriatric patients.

Polypharmacy and Comorbid Medical Illness

In selecting an agent to treat a psychotic disorder in an older patient, it is important to consider comorbid medical conditions that occur much more commonly in this population, such as cardiovascular disease, diabetes, and urinary retention, as well as other medications the patient may be taking. Because older patients are frequently treated with multiple medications, with the number of medications increasing significantly with age,[30–32] clinicians need to be especially alert for potential drug-drug interactions (DDIs) when using antipsychotics in older patients.

The labeling of all the SGAs contains a black box warning concerning an increased mortality rate in elderly patients with dementia-related psychosis, primarily due to cardiovascular or infectious causes. Several studies have reported an increased risk of serious adverse events or death in older patients with dementia who are treated with antipsychotics.[33–35] For more discussion of these issues, see the case of Mr. B below as well as the *Expert Consensus Guideline Series: Treatment of Dementia and Its Behavioral Disturbances*.[11] Although none of the SGAs are approved for the treatment of dementia-related psychosis, clinicians should keep these data in mind when using antipsychotics to treat other types of psychosis in elderly patients.

Applying the Roadmap Principles in the Treatment of Older Patients

Ms. A: A Widow With Unexplained Somatic Symptoms

Ms. A, an 85-year-old widow, presents to her internist complaining

Reprinted with correction to page 131.

of headaches and stomachaches of indeterminate duration. The patient has type 2 diabetes, which is well controlled with sitagliptin; mild hypertension, for which she takes a potassium-sparing diuretic; and mild osteoarthritis. A careful medical history and physical examination reveal no other problems that could account for her symptoms. The internist prescribes analgesics and asks the patient to return in 1 week unless the symptoms worsen.

Two days later, Ms. A calls the office to say that her headaches and stomachaches are worse. She insists on coming back in right away. During this visit, she tells the doctor for the first time that she is having trouble sleeping, has no appetite, and cannot concentrate when she tries to read the newspaper. Although the patient has always been carefully groomed and nicely dressed when seen in the past, she is dressed in a careless manner in wrinkled clothes. She says it is too much trouble to prepare meals, since she has no appetite anyway, and that, if she does feel hungry, she just opens a can and eats the food cold. She reports that her house is a mess but she does not have the energy to run the vacuum cleaner or wash the dishes. She says she lies awake at night for hours worrying about her daughter being an "old maid" and feeling very guilty because she thinks her daughter may not have married because she was always warning her to be careful about whom she married. She also reports feeling overwhelming guilt about a family in the neighborhood who recently moved away. She says she is sure they moved because of things she said to them about their children being noisy and leaving their bicycles in front of the house. She also says that she thinks her neighbors may be watching her and calling her daughter to report on her behavior.

Because the internist cannot find any physical problems to account for Ms. A's complaints, she performs a mental status examination. The patient's memory appears unimpaired (she can remember 3 objects in 3 minutes). However, the examination reveals that the patient is having difficulty with similarities and abstractions (e.g., she cannot identify how a banana and an orange or a poem and a statue are similar). Her performance on the clock drawing test shows difficulties in planning. When asked to draw the hands to show 11:10, she can do this, although slowly, but when asked to place the numbers on the clock, she spaces the numbers unequally. Yet, when the internist draws the clock, she can quickly copy it correctly. Because these findings suggest the patient has executive dysfunction rather than difficulties with construction, the internist orders magnetic resonance imaging (MRI) of the brain to evaluate for problems in the frontal and subcortical areas. The MRI shows mild atrophy consistent with age and nonspecific hyperintensities in the frontal lobe white matter.

Why did the internist order imaging studies of the brain? In a younger person with a negative medical history and physical examination, imaging studies might not have been necessary. However, in elderly patients, a variety of problems can masquerade as depression, and it is reasonable to be especially cautious in evaluating all possibilities.

The internist suspects the patient is suffering from a psychotic depression and makes a referral to a psychiatrist. The psychiatrist to whom Ms. A is referred questions her about a personal or family history of depression, and she denies both. He diagnoses a major depressive episode with psychotic features, determines that Ms. A is not suicidal, and starts the patient on the selective serotonin reuptake inhibitor (SSRI) paroxetine (20 mg/day) and the SGA risperidone (2 mg/day).

What do the findings from the examination and MRI tell us? Recent research indicates that white matter hyperintensities are common in elderly patients with depression, especially those with cardiovascular abnormalities such as hypertension, and that such hyperintensities may be associated with deficits in executive functioning.[36–38] A recent study found that elderly patients with microstructural white matter abnormalities on MRI are less likely to respond to treatment with SSRIs than those without such abnormalities.[39] Depressed older adults with executive dysfunction have also been found to have lower remission and response rates than patients without such dysfunction.[40]

Why did the psychiatrist begin with an SSRI plus an antipsychotic? Ms. A appeared to be experiencing psychotic symptoms. Psychotic depression in the elderly is particularly likely to manifest as guilty thoughts. The recommended initial treatment for psychotic depression in an elderly patient is an antidepressant plus an SGA.[10,41] When asked about the appropriateness of different antipsychotics to treat acute psychotic symptoms in patients 65 years and older, the Roadmap experts gave very similar ratings as for a healthy younger adult, with all the non-clozapine SGAs favored over older conventional antipsychotics, with highest ratings given to aripiprazole and risperidone, followed by ziprasidone.

Even though the patient denied feeling suicidal, should the psychiatrist have admitted her to the hospital to ensure her safety? This is a good question. The psychiatrist contacted the patient's daughter, who insisted that her mother stay with her until her symptoms improved. The psychiatrist also asked Ms. A to see him weekly and encouraged the patient and her daughter to call immediately if there was any change for the worse.

The psychiatrist continues to see the patient weekly. After 2 weeks, her mood is improved, but she continues to ruminate excessively about her guilty feelings. The daughter, who accompanies her mother to the appointment, reports that her mother is refusing to talk on the phone with family members because she believes the line is tapped. Given Ms. A's persistent symptoms of excessive guilt and paranoia, the psychiatrist slowly increases the risperidone to 4 mg/day over the next 2 weeks.

Reprinted with correction to page 131.

Shortly after Ms. A reaches a dose of 4 mg/day, her daughter calls to report that her mother is much calmer and less agitated, has been worrying less and sleeping better, and has resumed speaking to her family on the phone. However, about a week later, Ms. A's daughter calls in a panic to report that her mother's movements have become very slow and stiff, that she is tremulous, and that she has started drooling.

If you were the psychiatrist, what would you do at this point? As noted above, drugs are an important cause of acquired biological variance that can change response to concomitantly prescribed drugs.[15] Drugs can interact pharmacodynamically (e.g., EPS due to additive effects of 2 D_2 receptor blockers) and/or pharmacokinetically (e.g., effects on metabolism and/or clearance and thus accumulation of another drug). The most common clinically important pharmacokinetic DDIs involve effects on phase one (oxidative) metabolism via the cytochrome P450 (CYP) enzyme system responsible for the clearance of most drugs.[15] For example, coadministration of a substantial CYP2D6 inhibitor (bupropion, fluoxetine, or paroxetine) can increase risk of acute EPS in patients treated with risperidone by making genetically normal metabolizers functionally deficient in CYP2D6.[42] Ms. A's psychiatrist suspects that such an interaction may be responsible for what is happening in this case—that Ms. A's risperidone level is too high due to coadministration of paroxetine and that this is causing the EPS.

Should the psychiatrist adjust the dose of one of the drugs or switch to a different antidepressant or antipsychotic? As shown in Figure 2, a minimum threshold of 50% antagonism (blockade) of the D_2 receptor appears to be required for antipsychotic efficacy, while blockade greater than 80% appears to be associated with a markedly increased risk of EPS. This explains the relatively narrow window between antipsychotic efficacy and risk of acute EPS associated with unopposed D_2 antagonism. Ms. A experienced good amelioration of her psychotic symptoms but developed distressing EPS on 4 mg/day of risperidone (probably the equivalent of a considerably higher dose given the effect of paroxetine on risperidone's metabolism).

Ms. A's psychiatrist lowers the dose of risperidone to 1 mg/day for 3 days to see if the patient's response can be maintained at this dose. He decides not to prescribe benztropine, because anticholinergic agents are very likely to induce delirium in older patients. Two weeks later, Ms. A's EPS have resolved. However, although she has not relapsed, she is not completely free of psychotic symptoms. The psychiatrist increases the dose of risperidone to 2 mg/day. A week later, the daughter reports significant improvement in her mother's mood and guilty ruminations. Thus, at a dose of 4 mg/day of risperidone, given in combination with paroxetine, the patient had reached a level of risperidone above the 80% threshold for EPS. At a dose of 2 mg/day, the level was sufficient to maintain a good response but below that which would trigger EPS.

What other options could the psychiatrist have considered? If the patient could not maintain remission at a lower dose of risperidone (i.e., that did not cause EPS), the doctor could have switched to a different SGA with less liability for EPS. Or, since the patient has had a good response to one SSRI, he could have switched her to another SSRI that does not substantially inhibit CYP2D6 (e.g., sertraline, citalopram, escitalopram) and would not affect risperidone levels. This case illustrates the importance of considering the other medications a patient is taking when adding, changing, or adjusting the dose of psychiatric medications.[13,15] For more information on DDIs involving psychiatric drugs, see Preskorn and Flockhart.[14]

Mr. B: A Nursing Home Patient With Dementia

Mr. B is a 91-year-old man living in a nursing home who was diagnosed with probable Alzheimer's disease 6 years earlier. One year ago, because of his tendency to unpredictably leave his home, wander through his neighborhood, and get lost, Mr. B's family decided it would be safer to move him to a nursing home. Mr. B's medical history is significant for hypertension, a myocardial infarction 15 years ago, and a remote history of cigarette smoking. His current medications include donepezil, memantine, low-dose aspirin, a β-blocker, hydrochlorothiazide, sertraline 50 mg/day for depressive symptoms, a stool softener, and zolpidem for sleep. Mr. B can walk on his own; however, his gait is unsteady, and he gets confused about where he is and must always be accompanied.

Mr. B has recently begun exhibiting increasingly aggressive and paranoid behavior. He insists that the staff at the nursing home are stealing his things from his drawers, frequently screams at staff, and cries almost every night. He has several times accused his wife of 45 years of having an affair with another man, and he once pushed her, although he was too weak to hurt her. He has also become combative with staff when they try to help him with meals or showering. On one occasion, he became very agitated and suddenly pulled away from a staff member and fell. Fortunately, he did not sustain any fractures. The nursing home staff are concerned about Mr. B's safety and their ability to care for him and have asked for a psychiatric consultation.

What should the psychiatrist do? Reevaluation of the patient's mental status is imperative. A sudden worsening in mental status should alert the physician to the possibility of a medical contributor. A multitude of problems, including diarrhea and dehydration, hyponatremia, confusion related to diabetes, hypertension, space occupying lesions in the head, or a DDI, could cause the behavioral changes manifested in this case. Thus, the psychiatrist's first step is to evaluate for physical abnormalities and drug effects.

Reprinted with correction to page 131.

The adverse effects of the SSRIs are generally the same in younger and older patients. However, the risk of hyponatremia with SSRIs does increase with age. Suspecting a metabolic problem, the psychiatrist discontinues the sertraline and stool softener and orders a metabolic panel and complete blood count. The results of the laboratory tests reveal mild anemia (red blood cell count of 3.8) and mild hyponatremia. The psychiatrist advises the staff to restrict Mr. B's water intake and orders a hematology consult. Given that Mr. B's reticulocyte and platelet counts, vitamin B_{12} and folate levels, and electrolytes are within normal limits, the hematologist concludes that Mr. B is not losing blood and has no vitamin or iron deficiency that requires treatment. He diagnoses mild late-life anemia and recommends no intervention.

Repeat laboratory workup 2 weeks later indicates that the hyponatremia has resolved. However, Mr. B's agitation and behavioral problems persist, and the staff continue to express concerns about caring for him.

What interventions might the psychiatrist consider to treat the patient's behavioral abnormalities? The answer to this question has recently become more complicated. A very common intervention had previously been to prescribe low doses of an SGA. A meta-analysis of data from 15 randomized, placebo-controlled trials that compared SGAs (aripiprazole, olanzapine, quetiapine, and risperidone) (N = 3353) with placebo (N = 1757) in treatment of patients with dementia found a small increased risk of death with SGAs compared with placebo.[43] Three other large population-based studies reported increased risk for serious adverse events or death in older adults with dementia treated with antipsychotics compared with those not treated with antipsychotics.[33–35] These studies found that patients treated with SGAs had a slightly higher risk of mortality but that the risk with conventional antipsychotics was at least as high, if not higher. Thus, these findings do not support the use of conventional antipsychotics (e.g., haloperidol) in place of SGAs. In interpreting these findings, clinicians should take into account that, although these studies attempted to adjust for differences in baseline health status, patients who were more likely to be prescribed an antipsychotic may have been more seriously ill (e.g., more likely to have delirium and dementia). The reason for the slightly increased mortality risk in demented patients treated with antipsychotics is uncertain, and more data are needed. Nevertheless, physicians have become more circumspect about prescribing SGAs for older patients with dementia.

A number of other agents have been investigated as alternatives to manage behavioral problems in dementia. Extensive research has focused on mood stabilizing drugs. However, valproate has not been found to be effective, while carbamazepine may be effective for behavioral symptoms in dementia. A single randomized trial comparing citalopram and risperidone for treatment of agitation and psychotic symptoms in nondepressed patients with dementia reported promising results for citalopram,[44] but these findings need to be replicated.

The psychiatrist decides to prescribe a low-dose SGA for Mr. B. What is the rationale for this decision? In selecting a treatment for a patient such as Mr. B, the psychiatrist must consider the risk-benefit equation. The risks associated with SGAs needs to be considered in the context of medical need for the drug, evidence for its efficacy, medical comorbidity, and the efficacy and safety of alternatives.[43] Mr. B has a history of falls, and if his agitated and combative behavior continues, he may well fall again and sustain a serious injury. In addition, the staff is unable to bathe or feed Mr. B adequately in his current state.

The psychiatrist concludes that letting Mr. B's behavior continue untreated poses a greater risk to his health and welfare than the risks associated with treatment with an SGA. He starts Mr. B on treatment with olanzapine 5 mg/day. A week later, staff report a marked improvement in his behavior.

Mr. C: An Older Man With Chronic Schizophrenia

Mr. C is a 67-year-old man who has a history of chronic schizophrenia, with episodes of delusions and bizarre behavior when not taking medication that have led to multiple hospitalizations. The patient lives with his sister, who is responsible for his care, and has been followed for many years at the local Community Mental Health Center. The patient was treated with haloperidol 10 mg/day for 15 years. However, because he had EPS that were poorly controlled by benztropine and had developed mild tardive dyskinesia (difficulty swallowing), the patient was switched to olanzapine 10 mg/day 18 months ago. Olanzapine controlled the patient's delusions and bizarre behavior, and his EPS were much reduced, allowing him to begin work in a sheltered carpentry shop, which he very much enjoyed. However, the patient has gained a significant amount of weight since beginning olanzapine treatment, and his current body mass index is 33.0. His laboratory results over the past 12 months have shown rising lipid levels, and the most recent results also showed elevated blood sugar levels.

The patient's case manager at the Community Mental Health Center calls you for a consultation. What do you recommend? In deciding on a treatment strategy for a patient who has gained weight and developed metabolic abnormalities while taking an SGA, the Roadmap experts concluded that dose reductions are unlikely to help. Therefore, if these problems do not respond to changes in diet or lifestyle, the experts suggested switching to an agent with lower weight gain liability and metabolic risk[1] (Table 3).

The case manager reports that she has repeatedly encouraged Mr. C to make changes in diet and increase his exercise, but that he has not followed through with any of these recommendations. You suggest switching the patient from olanzapine to aripiprazole,

Reprinted with correction to page 131.

Table 3. Second Generation Antipsychotics and Metabolic Abnormalities[a]

Antipsychotic	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole[b]	+/–	–	–
Ziprasidone[b]	+/–	–	–

[a]Reprinted with permission from the American Diabetes Association.[12]
[b]Newer drugs with limited long-term data.
Symbols: + = increase effect, – = no effect, D = discrepant results.

Table 4. Sample Cross-Titration Schedule for Switching Older Patient From Olanzapine to Aripiprazole

Week	Olanzapine	Aripiprazole
1	7.5 mg/d	2 mg/d
2	7.5 mg/d	5 mg/d
3	5 mg/d	7 mg/d
4	2.5 mg/d	10 mg/d
5	0	12 mg/d

using a very gradual cross-titration and aiming for a target dose of 12 mg/day (Table 4). You ask the case manager to advise the patient and his sister to call the clinic if he should have any problems with agitation or insomnia, in which case you can prescribe a sedative for short-term use during the switch.

The Roadmap experts noted that the best way to minimize early agitation and insomnia with aripiprazole is to increase the dose very slowly and try to use the lowest possible effective dose. For a review of metabolic effects of SGAs, see Newcomer.[45] For recommendations on monitoring weight and metabolic problems in patients treated with antipsychotics, see the 2004 statement from the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes.[12]

Ms. D: A Patient With Psychotic Mania

Ms. D is a 73-year-old woman with bipolar disorder who is admitted to the hospital for what is initially diagnosed as an episode of acute mania with psychosis. She has been maintained on lithium for many years, and has also received antidepressants and antipsychotics at various times. The patient is brought in by her daughter, who reports that Ms. D has recently become very agitated, irritable, and hyperactive; her behavior has been very disorganized; and she has not been sleeping. The daughter believes it is an exacerbation of mania and insists that the doctor increase the lithium dose. During the initial evaluation, the patient appears confused and disoriented and is unable to correctly state the date or day of the week.

The inpatient psychiatrist suspects the patient may be displaying lithium-related delirium rather than mania. The psychiatrist tells the patient's daughter that she wants to stop lithium treatment, prescribe an SGA (quetiapine) to calm the patient, and obtain a lithium level and laboratory workup. When she explains to the daughter that continuing the lithium if it is causing toxicity could be dangerous, the daughter agrees to the change.

The psychiatrist orders a lithium level as well as electrolytes, thyroid panel, and a complete blood count. The patient's lithium level is 2.1 mEq/L. The laboratory results indicate that the patient's renal function is compromised (serum creatinine 2.5 mg/dL, bilirubin 40 μmol/L, creatinine clearance 45 mL/min), accounting for the toxic level of lithium. A nephrology consult is requested. The nephrologist suggests that he follow the patient closely for a month to see if the values improve and advises avoiding any medications metabolized primarily by the kidney (e.g., memantine). Once the patient is stabilized and her confusion improves, the psychiatrist discontinues quetiapine treatment and starts divalproex treatment, to which Ms. D responds well.

In this case, the patient's unrecognized kidney failure represented variable 3 in the equation in Figure 1. It is important for clinicians to keep in mind that individual biological factors, such as comorbid medical conditions and concomitant medications, frequently change, especially in older patients, which may necessitate adjustments in the patient's treatment regimen.

Conclusion

The Roadmap recommendations for using antipsychotics are based on the principle that best outcomes can be achieved by considering risks and benefits of each treatment option in the context of the individual patient's diagnosis (primary psychiatric illness and comorbid psychiatric and medical conditions), current symptoms, illness and treatment history, age, gender, and psychosocial situation, as well as personal goals and preferences. Achieving best outcomes involves balancing risks and benefits, and trade-offs often have to be made.[1,46] Since no available treatments are free of adverse effects, a better understanding of pharmacologic principles and of the properties of the different agents and how they are likely to interact with the patient's individual characteristics can help clinicians maximize efficacy while minimizing side effects. This article highlights issues that commonly arise in the use of antipsychotic medications in older patients, who are especially likely to have 1 or more complicating medical conditions, to be taking multiple medications, and to have reduced metabolic functioning.

Drug names: aripiprazole (Abilify), benztropine (Cogentin), bupropion (Wellbutrin), citalopram (Celexa and others), divalproex (Depakote), donepezil (Aricept), escitalopram (Lexapro), fluoxetine (Prozac and others), haloperidol (Haldol and others), hydrochlorothiazide (Oretic, Microzide, and others), lithium (Eskalith, Lithobid, and others), memantine (Namenda), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft and others), sitagliptin (Januvia), ziprasidone (Geodon), zolpidem (Ambien).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, second-generation antipsychotics are not

Reprinted with correction to page 131.

approved by the U.S. Food and Drug Administration for the treatment of dementia.

REFERENCES

1. Weiden PJ, Preskorn SH, Fahnestock PA, et al. Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap. J Clin Psychiatry 2007;68(suppl 7):1–48
2. Colenda CC, Mickus MA, Marcus SC, et al. Comparison of adult and geriatric psychiatric practice patterns: findings from the American Psychiatric Association's Practice Research Network. Am J Geriatr Psychiatry 2002;10:609–617
3. Ruths S, Straand J, Nygaard HA. Multidisciplinary medication review in nursing home residents: what are the most significant drug-related problems? the Bergen District Nursing Home (BEDNURS) study. Qual Saf Health Care 2003;12:176–180
4. Field TS, Gurwitz JH, Avorn J, et al. Risk factors for adverse drug events among nursing home residents. Arch Intern Med 2001; 161:1629–1634
5. The President's New Freedom Commission on Mental Health. Achieving the Promise: Transforming Mental Health Care in America. Final Report. Department of Health and Human Services Publication No. SMA-03–3832. Rockville, Md: Department of Health and Human Services; 2003. Available at: www.mentalhealthcommission.gov/reports/finalreport/fullreport-02.htm
6. Lehman AF, Lieberman JA, Dixon LB, et al. Practice Guideline for the Treatment of Patients With Schizophrenia, Second Edition. Am J Psychiatry 2004 Feb; 161(suppl 2):1–56
7. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder (Revision). Am J Psychiatry 2002 Apr;159(suppl 4):1–50
8. Kane JM, Leucht S, Carpenter D, et al. The Expert Consensus Guideline Series: Optimizing Pharmacologic Treatment of Psychotic Disorders: introduction: methods, commentary, and summary. J Clin Psychiatry 2003;64(suppl 12):5–19
9. Keck PE, Perlis RH, Otto MW, et al. The Expert Consensus Guideline Series: Treatment of Bipolar Disorder 2004. Postgrad Med Spec Rep 2004:1–120
10. Alexopoulos GS, Streim J, Carpenter D, et al. The Expert Consensus Guideline Series: Using Antipsychotic Medications in Older Patients. J Clin Psychiatry 2004; 65(suppl 2):5–99
11. Alexopoulos GS, Jeste DV, Chung H, et al. The Expert Consensus Guideline Series: Treatment of Dementia and Its Behavioral Disturbances. Postgrad Spec Rep January 2005:1–108
12. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. J Clin Psychiatry 2004;65(2):267–272
13. Preskorn SH. How multiple medication use evolves and the importance of therapeutic trials: the slippery slide. J Psychiatr Pract 2008;14:170–175
14. Preskorn SH, Flockhart DA. 2006 Guide to psychiatric drug interactions. Prim Psychiatry 2006;13:35–64. Available at: http://www.primarypsychiatry.com/aspx/articledetail.aspx?articleid=338
15. Levy RH, Thummel KE, Trager WF, et al. Metabolic Drug Interactions. Philadelphia, Pa: Lippincott, Williams & Wilkins; 2000
16. Preskorn SH. Classification of neuropsychiatric medications by principal mechanism of action: a meaningful way to anticipate pharmacodynamically mediated drug interactions, pt 1. J Psychiatr Pract 2003;9: 376–384
17. Preskorn SH. Classification of neuropsychiatric medications by principal mechanism of action: a meaningful way to anticipate pharmacodynamically mediated drug interactions, pt 2. J Psychiatr Pract 2004;10: 177–181
18. Gardner DM, Baldessarini RJ, Waraich P. Modern antipsychotic drugs: a critical overview. CMAJ 2005;172:1703–1711
19. Richelson E. Pharmacology of antidepressants. Mayo Clinic Proc 1994;69:1069–1081
20. Abilify [package insert]. Princeton, NJ: Bristol-Myers Squibb Co; 2006
21. Arnt J, Skarsfeldt T. Do novel antipsychotics have similar pharmacological characteristics? Neuropsychopharmacology 1998;18:63–101
22. Bymaster FP, Hemrick-Luecke SK, Perry KW, et al. Neurochemical evidence for antagonism by olanzapine of dopamine, serotonin, alpha 1-adrenergic and muscarinic receptors in vivo in rats. Psychopharmacology (Berl) 1996; 124:87–94
23. Seeger TF, Seymour PA, Schmidt AW, et al. Ziprasidone (CP-88,059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. J Pharmacol Exp Ther 1995;275:101–113
24. Seroquel [package insert]. Wilmington, Del: AstraZeneca Pharmaceuticals; 2007, 2008. Available at: www1.astrazeneca-us.com/pi/seroquel.pdf
25. Weiden PJ. Switching in the era of atypical antipsychotics: an updated review. Postgrad Med 2006 Sep;Spec No:27–44
26. Nyberg S, Farde L, Halldin C. Test-retest reliability of central [11C]raclopride binding at high D2 receptor occupancy: a PET study in haloperidol-treated patients. Psychiatry Res 1996;67:163–171
27. Frankle WG, Gil R, Hackett E, et al. Occupancy of dopamine D2 receptors by the atypical antipsychotic drugs risperidone and olanzapine: theoretical implications. Psychopharmacology (Berl) 2004;175: 473–480
28. Preskorn SH. Defining "is." J Pract Psychiatry Behav Health 1999;5:224–228
29. AmpliChip CYP450 Test [package insert]. Branchburg, NJ: Roche Molecular Systems; 2006. Available at: http://www.amplichip.us/ documents/CYP450_P.I._USIVD_Sept_15_2006.pdf
30. Bjerrum L, Sogaard J, Hallas J, et al. Polypharmacy: correlations with sex, age and drug regimen: a prescription database study. Eur J Clin Pharmacol 1998;54:197–202
31. Rosholm JU, Bjerrum L, Hallas J, et al. Polypharmacy and the risk of drug-drug interactions among Danish elderly: a prescription database study. Dan Med Bull 1998;45: 210–213
32. Preskorn SH, Silkey B, Shah R, et al. Complexity of medication use in the Veterans Affairs healthcare system, pt 1: outpatient use in relation to age and number of prescribers. J Psychiatr Pract 2005;11:5–15
33. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs atypical antipsychotic medications. N Engl J Med 2005;353:2335–2341
34. Gill SS, Bronskill SE, Normand SL, et al. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med 2007; 146(11):775–786
35. Rochon PA, Normand SL, Gomes T, et al. Antipsychotic therapy and short-term serious events in older adults with dementia. Arch Intern Med 2008;168:1090–1096
36. Gunning-Dixon FM, Hoptman MJ, Lim KO, et al. Macromolecular white matter abnormalities in geriatric depression: a magnetization transfer imaging study. Am J Geriatr Psychiatry 2008;16:255–262
37. Hoptman MJ, Gunning-Dixon FM, Murphy CF, et al. Blood pressure and white matter integrity in geriatric depression [published online ahead of print Sept 19, 2008]. J Affect Disord. doi:10.1016/j.jad.2008.07.024
38. Gunning-Dixon FM, Brickman AM, Cheng JC, et al. Aging of cerebral white matter: a review of MRI findings [published online ahead of print July 21, 2008]. Int J Geriatr Psychiatry. doi:10.1002/gps.2087
39. Alexopoulos GS, Murphy CF, Gunning-Dixon FM, et al. Microstructural white matter abnormalities and remission of geriatric depression. Am J Psychiatry 2008;165: 238–244
40. Alexopoulos GS, Kiosses N, Heo M, et al. Executive dysfunction and the course of geriatric depression. Biol Psychiatry 2005; 58:204–210
41. Alexopoulos GS, Katz IR, Reynolds CF 3rd, et al. The Expert Consensus Guidelines: Pharmacotherapy of Depressive Disorders in Older Patients. Postgrad Med 2001 Oct;Spec No Pharmacotherapy:1–86
42. de Leon J, Susce MT, Pan RM, et al. The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation. J Clin Psychiatry 2005;66(1):15–27
43. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934–1943
44. Pollock BG, Mulsant BH, Rosen J, et al. A double-blind comparison of citalopram and risperidone for the treatment of behavioral and psychotic symptoms associated with dementia. Am J Geriatr Psychiatry 2007;15:942–952
45. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 2005;19(suppl 1):1–93
46. Weiden PJ, Buckley PF. Reducing the burden of side effects during long-term antipsychotic therapy: the role of "switching" medications. J Clin Psychiatry 2007;68(suppl 6):12–23

For the CME Posttest for this ACADEMIC HIGHLIGHTS, see pages 148–149.

Reprinted with correction to page 131.