

Introduction: Methods, Commentary, and Summary

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ABSTRACT

Objectives. Antipsychotics are widely used in geriatric psychiatric disorders. A growing number of atypical antipsychotics are available, expanding clinical options but complicating decision-making. Many questions about use of antipsychotics in older patients remain unanswered by available clinical literature. We therefore surveyed expert opinion on antipsychotic use in older patients (65 years of age or older) for recommendations concerning indications for antipsychotics, choice of antipsychotics for different conditions (e.g., delirium, dementia, schizophrenia, delusional disorder, psychotic mood disorders) and for patients with comorbid conditions or history of side effects, dosing strategies, duration of treatment, and medication combinations.

Method. Based on a literature review, a 47-question survey with 1,411 options was developed. Approximately three quarters of the options were scored using a modified version of the RAND 9-point scale for rating appropriateness of medical decisions. For other options, experts were asked to write in answers. The survey was sent to 52 American experts on treatment of older adults (38 geriatric psychiatrists, 14 geriatric internists/family physicians), 48 (92%) of whom completed it. In analyzing responses to items rated on the 9-point scale, consensus was defined as a nonrandom distribution of scores by chi-square "goodness-of-fit" test. We assigned a categorical rank (first line/preferred, second line/alternate, third line/usually inappropriate) to each option based on the 95% confidence interval around the mean. Guidelines indicating preferred treatment strategies were then developed for key clinical situations.

Results. The expert panel reached consensus on 78% of options rated on the 9-point scale. The experts *did not recommend* using antipsychotics in panic disorder, generalized anxiety disorder, nonpsychotic major depression, hypochondriasis, neuropathic pain, severe nausea, motion sickness, or irritability, hostility, and sleep disturbance in the absence of a major psychiatric syndrome. However, antipsychotics were favored in several other disorders. For *agitated dementia with delusions*, the experts' first-line recommendation is an antipsychotic drug alone; they would also consider adding a mood stabilizer. Risperidone (0.5–2.0 mg/day) was first line followed by quetiapine (50–150 mg/day) and olanzapine (5.0–7.5 mg/day) as high second-line options. There was no first-line recommendation for *agitated dementia without delusions*; an antipsychotic alone was high second line (rated first line by 60% of the experts). The experts' first-line recommendation for late-life *schizophrenia* was risperidone (1.25–3.5 mg/day), quetiapine (100–300 mg/day), olanzapine (7.5–15 mg/day), and aripiprazole (15–30 mg/day) were high second line. For older patients with *delusional disorder*, an antipsychotic was the only treatment recommended. For *agitated nonpsychotic major depression* in an older patient, the experts' first-line recommendation was an antidepressant alone (77% first line); second-line options were an antidepressant plus an antipsychotic, electroconvulsive therapy (ECT), an antidepressant plus a benzodiazepine, and an antidepressant plus a mood stabilizer. For *nonpsychotic major depression with severe anxiety*, the experts recommended an antidepressant alone (79% first line) and would also consider adding a benzodiazepine or mood stabilizer to the antidepressant. If an older patient with

nonpsychotic major depression fails to respond to antidepressants at adequate dosages for adequate duration, there was limited support for adding an atypical antipsychotic to the antidepressant (36% first line after two failed antidepressant trials). Treatment of choice for *geriatric psychotic major depression* was an antipsychotic plus an antidepressant (98% first line), with ECT another first-line option (71% first line). For *mild geriatric nonpsychotic mania*, the first-line recommendation is a mood stabilizer alone; the experts would also consider discontinuing an antidepressant if the patient is receiving one. For *severe nonpsychotic mania*, the experts recommend a mood stabilizer plus an antipsychotic (57% first line) or a mood stabilizer alone (48% first line) and would discontinue any antidepressant the patient is receiving. For *psychotic mania*, treatment of choice is a mood stabilizer plus an antipsychotic (98% first line). Risperidone (1.25–3.0 mg/day) and olanzapine (5–15 mg/day) were first-line options in combination with a mood stabilizer for mania with psychosis, with quetiapine (50–250 mg/day) high second line. If a patient has responded well, the experts recommended the following duration of treatment before attempting to taper and discontinue the antipsychotic: delirium, 1 week; agitated dementia, taper within 3–6 months to determine the lowest effective maintenance dose; schizophrenia, indefinite treatment at the lowest effective dose; delusional disorder, 6 months–indefinitely at the lowest effective dose; psychotic major depression, 6 months; and mania with psychosis, 3 months.

For patients with diabetes, dyslipidemia, or obesity, the experts would avoid clozapine, olanzapine, and conventional antipsychotics (especially low- and mid-potency). Quetiapine is first line for a patient with Parkinson's disease. Clozapine, ziprasidone, and conventional antipsychotics (especially low- and mid-potency) should be avoided in patients with QTc prolongation or congestive heart failure. For patients with cognitive impairment, constipation, diabetes, diabetic neuropathy, dyslipidemia, xerophthalmia, and xerostomia, the experts prefer risperidone, with quetiapine high second line. More than a quarter of the experts considered these combinations contraindicated: clozapine + carbamazepine, ziprasidone + tricyclic antidepressant (TCA), and a low-potency conventional antipsychotic + fluoxetine. In combining antidepressants and antipsychotics, the experts would be much more cautious with selective serotonin reuptake inhibitors that are more potent inhibitors of the CYP 450 enzymes (i.e., fluoxetine, fluvoxamine, paroxetine) and with nefazodone, TCAs, and monoamine oxidase inhibitors. The experts recommended extra monitoring when combining any antipsychotic with lithium, carbamazepine, lamotrigine, or valproate (except aripiprazole, risperidone, or a high-potency conventional plus valproate) or with codeine, phenytoin, or tramadol.

Conclusions. The experts reached a high level of consensus on many of the key treatment questions. Within the limits of expert opinion and with the expectation that future research data will take precedence, these guidelines provide direction for common clinical dilemmas in the use of antipsychotics in elderly patients. Clinicians should keep in mind that no guidelines can address the complexities of an individual patient and that sound clinical judgment based on clinical experience should be used in applying these recommendations.

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WHY DO WE NEED GUIDELINES ON THE USE OF ANTIPSYCHOTICS IN OLDER PATIENTS?

Antipsychotics are widely used in older patients to treat a variety of psychiatric disturbances. A study using data from the American Psychiatric Association's Practice Research Network compared treatment patterns in patients under and over age 65.¹ This study found a disproportionately high use of antipsychotics and antianxiety/benzodiazepine medications among geriatric patients compared with those under age 65. They also found a higher Axis III comorbidity (i.e., general medical conditions) among older patients receiving psychiatric care than younger patients. A recent multidisciplinary review examined drug use in 1,354 nursing home residents in 23 nursing homes in Bergen, Norway, in 1997.² This study identified 2,445 potential medication problems in 1,036 residents (76%). Psychoactive drugs accounted for 38% of all problems, with antipsychotics the class most often involved. Use of multiple psychoactive drugs was found to be particularly troublesome. Problems related to psychotropic polypharmacy included adverse drug reactions (26%), inappropriate drug choices (20%), and use of non-therapeutic dosages (13%). Another prospective study examined adverse drug events among the residents of 18 nursing homes.³ This study found that adverse drug events occurred in 410 (14%) of 2,916 long-term care patients and that one of the independent risk factors for adverse events was taking antipsychotics (OR 3.2). Of the 410 residents who experienced adverse drug events, 226 (55%) had at least one preventable event, and taking antipsychotics was also an independent risk factor for such events (OR 4.0).

These findings demonstrate that antipsychotics are widely used in older patients and are a frequent source of problems. In response to this concern, we conducted a survey study of expert opinion on the use of the antipsychotics in the elderly to answer key questions that may not have been adequately addressed by the research literature. Guidance concerning the appropriate use of antipsychotics in the elderly is important for a number of reasons:

1. Many older patients with psychiatric disturbances are treated by internists, family physicians, general practitioners, or nurse practitioners, some of whom may not be thoroughly familiar with the use of antipsychotic agents.
2. Antipsychotic drugs are both overused and underused in elderly patients. Federal regulations have been imposed on nursing homes, with the intention of reducing the misuse of antipsychotic drugs in older adults. These regulations focus on the limitation of antipsychotic drug use, but there is little guidance for their therapeutic use.
3. Controlled trials to guide clinical decision-making in the use of antipsychotics in elderly patients are limited, and few studies with large numbers of subjects are available. The paucity of studies is not due to lack of clinical necessity but rather due to difficulties in undertaking clinical trials in this population (e.g., it is hard to locate and enroll an adequate number of appropriate patients).

4. As noted above, the clinical care of elderly patients is complex; elderly patients usually have multiple disorders, often take many different medications, and may be more sensitive to adverse drug effects than younger adults.
5. A growing number of atypical antipsychotics are available, enlarging clinicians' options but at the same time making clinical decisions more complex.

METHOD OF DEVELOPING EXPERT CONSENSUS GUIDELINES

The contribution of expert consensus to practice guideline development continues to evolve throughout medicine, alongside the "gold standard" of meta-analysis of clinical trials and other experimental data. The sheer number of possible combinations and sequences of available treatments for many diseases makes it difficult to provide comparative recommendations based entirely on clinical trial data.^{4,5} A method for describing expert opinion in a quantitative, reliable manner to help fill some of the gaps in evidence-based guidelines has been developed. This method has been applied to a variety of psychiatric disorders.⁶⁻¹⁸

Creating the Surveys

In this survey study, we first created a skeleton algorithm based on a literature review. We sought to identify key decision points in the use of antipsychotics in older patients as well as a list of feasible treatment options. We highlighted important clinical questions that had not yet been adequately addressed or definitively answered in the literature.¹⁹ We then developed a questionnaire consisting of 47 questions and a total of 1,411 options. We asked about the most appropriate indications for using antipsychotics in older patients, the most salient features in diagnosing a variety of disorders in older patients, and recommendations for choosing specific antipsychotics for a variety of different conditions (e.g., delirium, dementia, schizophrenia, delusional disorder, psychotic and nonpsychotic major depression, and psychotic and nonpsychotic mania), for patients with various complicating conditions (e.g., diabetes, QTc prolongation, narrow angle glaucoma, osteoporosis), and for patients with a history of adverse effects associated with other medications (e.g., sedation, orthostatic hypotension, tardive dyskinesia). We also asked about dosing strategies, duration of treatment, and medication combinations that should be avoided or used very cautiously.

The Rating Scale

For approximately three quarters of the options in the survey, we asked raters to evaluate appropriateness by means of a 9-point scale slightly modified from a format developed by the RAND Corporation for ascertaining expert consensus.²⁰ For the other questions, we asked respondents to write in answers (e.g., the average acute target dose of a drug). We asked the experts to draw on both their knowledge of the research literature (we did not provide a literature review) and their best clinical judgment in making their ratings, but not to consider financial cost.

We presented the rating scale to the experts with the anchors shown in figure 1.

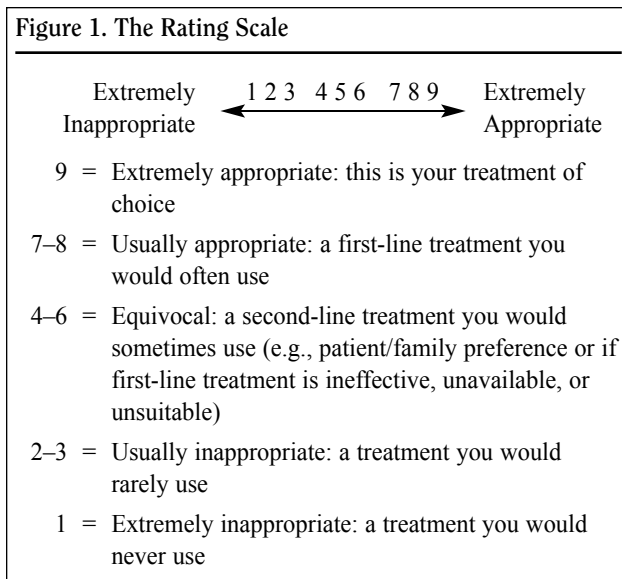
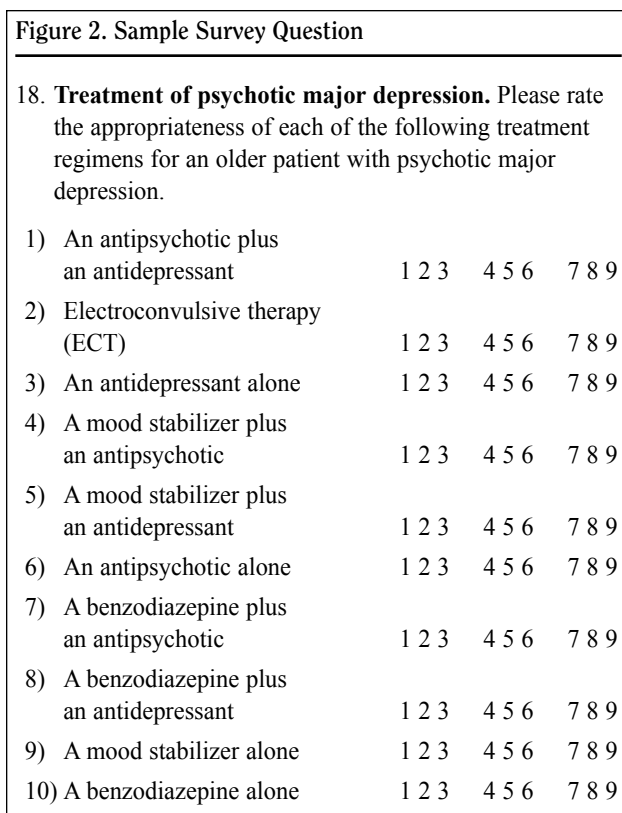


Figure 2 shows Survey Question 18 as an example of our question format.



Composition of the Expert Panel

We identified 52 leading American experts in the treatment of older adults: 38 geriatric psychiatrists and 14 geriatric internists/family physicians. The experts were identified from

several sources: recent research publications and funded grants, and participants in previous Expert Consensus surveys on the treatment of older patients.^{9,17} We provided a \$500 honorarium. Panelists reported taking 2 or more hours to complete the survey. This project was supported by an unrestricted grant from Janssen Pharmaceutica, L.P., to Comprehensive Neuroscience, Inc., the organization responsible for the administrative aspects of this study. The experts who completed the survey were kept blind to the sponsorship for this project in order to avoid bias.

We received responses from 48 (92%) of the 52 physician experts to whom the survey was sent (36 geriatric psychiatrists and 12 geriatric internists/family physicians). Of the respondents, 3 (6%) were female and 45 (94%) male. Their mean age was 50 years, with a mean of 21 years in practice; 40% reported spending at least half their work time and 46% about a quarter of their work time seeing patients. The majority of experts worked in an academic clinical or research setting, while 10% reported being in private practice and 13% indicated that they practice in the public sector. Of the 48 respondents, 58% had participated in a research project involving antipsychotics during the past 5 years, 65% had held a federal (NIMH or NIH) research grant as a principal investigator, and 69% had been principal investigator for an industry-sponsored grant.

Data Analysis for Options Scored on the Rating Scale

For each option, we first defined the presence or absence of consensus as a distribution unlikely to occur by chance by performing a chi-square test ($p < 0.05$) of the distribution of scores across the 3 ranges of appropriateness (1–3, 4–6, 7–9). Next we calculated the mean and 95% confidence interval (C.I.). A categorical rating of first, second, or third line was designated based on the lowest category in which the C.I. fell, with boundaries of 6.5 or greater for first line, and 3.5 up to 6.5 for second line. Within first line, we designated an item as “treatment of choice” if at least 50% of the experts rated it as 9.






Data Analysis for Write-In Options

For many questions concerning dosing, we asked respondents to write in their answers. This kind of question typically produces a number of extreme outlier responses. In analyzing the results of this type of question in this survey, we subjected these write-in responses to a Winsorizing(1) process,²¹ which involves replacing the highest and lowest responses to a question with the next highest and next lowest responses, respectively. In effect, Winsorizing has an impact on a distribution only if there is a single extreme outlier in either direction from the mean; in such situations, that extreme value is replaced with the next less extreme value. Our rationale for using this process was that a single extreme outlier might have interpreted the question differently than his or her peers—but that two extreme outliers would be less likely to have done so. Using the Winsorized data, means and standard deviations were calculated for each dosing question. The aggregate dosing values given in the guidelines are based on those means and standard deviations adjusted to the nearest available pill strength for each drug.

Displaying the Survey Results

The results of Question 18 (figure 2) are presented graphically in figure 3. The C.I.s for each treatment option are shown as horizontal bars and the numerical values are given in the table on the right. The ratings are represented graphically as shown below.

The Ratings

	Treatment of choice
	First line
	Second line
	Third line
	No consensus

First-line treatments are those strategies that came out on top when the experts' responses to the survey were statistically aggregated. These are options that the panel feels are usually appropriate as initial treatment for a given situation. Treatment of choice, when it appears, is an especially strong first-line recommendation (having been rated as "9" by at least half the experts). In choosing between several first-line recommendations, or deciding whether to use a first-line treatment at all, clinicians should consider the overall clinical situation, including the patient's prior response to treatment, adverse drug effects, general medical problems, and patient preferences.

Second-line treatments are reasonable choices for patients who cannot tolerate or do not respond to the first-line choices. A second-line choice might also be used for initial treatment if the first-line options are deemed unsuitable for a particular patient (e.g., because of poor previous response, inconvenient dosing regimen, particularly annoying side effects, general medical contraindication). For some questions, second-line ratings dominated, especially when the experts did not reach any consensus on first-line options. In such cases, to differentiate among the alternatives, we label those items whose C.I.s overlap with the first-line category as "high second line."

Third-line treatments are usually inappropriate or used only when preferred alternatives have not been effective.

No consensus. For each item in the survey, we used a chi-square test to determine whether the experts' responses were randomly distributed across the 3 categories, which suggests a lack of consensus. These items are indicated by an unshaded bar in the survey results.

Statistical differences between treatments. While we did not perform tests of significance for most treatments, the reader can readily see whether C.I.s overlap (roughly indicating no significant difference between options by *t*-test). The wider the gap between C.I.s, the smaller the *p* value would be (i.e., the more significant the difference). In some questions there are striking and important differences within levels, which we occasionally

point out. Often, however, differences within levels are not significant from a statistical perspective. Also, there are sometimes no statistical differences between choices at the bottom of first line and those at the top of second line.

From Survey Results to Guidelines

After the survey results were analyzed and ratings assigned, the next step was to turn these recommendations into user-friendly guidelines. We generally present two levels of recommendations: "preferred" (first line) and "also consider" (high second line, options on which the experts reached consensus with a mean rating of 5.6 or higher). Whenever the guideline lists more than one option in a rating level, we list the options in the order of their mean scores. As an example, the full results of the question presented above are shown on page 58 and are used in Guideline 7B.

Degree of Consensus

Of the 1,014 options rated on the 9-point scale, consensus was reached on 789 options (78%) as defined by the chi-square test. When there is no first-line recommendation, we choose the highest-rated second-line option as the "preferred" treatment and indicate this in the guideline.

RESULTS AND COMMENTARY

In the following sections, we summarize the key recommendations from the guidelines and consider how the experts' recommendations relate to the available research literature. The complete set of data from the survey is presented on pages 42–99. The guidelines derived from the data are presented on pages 21–41.

Indications for Using Antipsychotics in Older Patients

The experts agreed that antipsychotics are indicated for disorders with psychotic symptoms, i.e., schizophrenia, mania with psychosis, agitated dementia with delusions, psychotic major depression, and delusional disorder. They suggested that antipsychotics are sometimes indicated for mania without psychosis, delirium, and agitated dementia without delusions. Antipsychotics were low second-line choices in nonpsychotic major depression with agitation or with severe anxiety. The use of antipsychotics for these conditions may sometimes be appropriate, especially for patients with refractory depression.

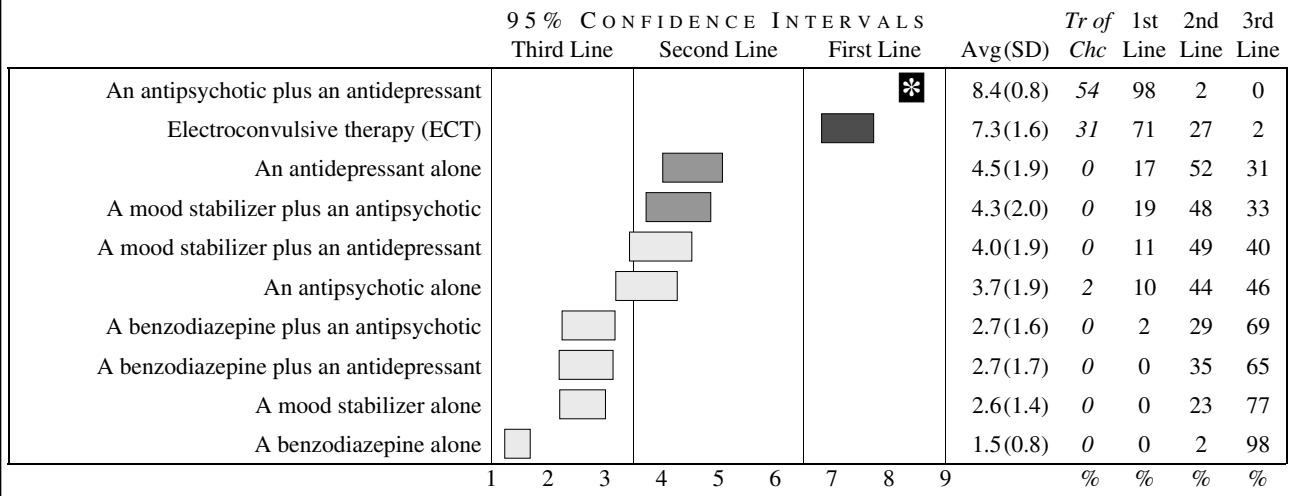
The experts would not recommend antipsychotics for panic disorder; generalized anxiety disorder; hypochondriasis; nonpsychotic major depression without severe anxiety; irritability, hostility, and sleep disturbance in the absence of a major psychiatric syndrome; severe nausea and vomiting (e.g., due to chemotherapy); neuropathic pain; or motion sickness.

Diagnosis, Medication Selection, and Dosing for Specific Indications

There are only a limited number of controlled clinical research trials with antipsychotics in elderly patients, and only

Figure 3. Graphic Results of Survey Question 18

18 Treatment of psychotic major depression. Please rate the appropriateness of each of the following treatment regimens for an older patient with psychotic major depression.



a few of those involved adequate numbers of patients. In the following sections, we will refer readers to relevant published trials, but clinicians should be alert for new research data as they become available.

Delirium. The features that the experts consider most important in diagnosing delirium reflect the criteria given in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*.²²

There was no consensus among the experts on a first-line antipsychotic drug for delirium. Risperidone 0.75–1.75 mg/day received high second-line ratings. Quetiapine received lower second-line ratings. Although high-potency conventional antipsychotics and olanzapine also received second-line ratings, there was no consensus on these options.

The recommendation for using atypical antipsychotics in delirium is supported by uncontrolled clinical studies.²³ In particular, Breitbart et al. conducted an open, prospective trial of olanzapine for the treatment of delirium in 79 hospitalized cancer patients and found that 76% had complete resolution of their delirium with olanzapine therapy.²⁴ No patients experienced extrapyramidal side effects (EPS) but 30% experienced sedation, although this was not severe enough to interrupt treatment. History of dementia, delirium due to central nervous system metastases and hypoxia, hypoactive or severe delirium, and age over 70 years were the most powerful predictors of poorer response to olanzapine treatment for delirium.

Dementia with agitation. The experts' responses suggested that several conditions may contribute to agitation in demented patients. Delirium was the single most important such condition (94% first line), followed by agitated depression (88% first line); 60% or more of the experts gave first-line ratings to pain, dysuria, dyspnea, and abdominal discomfort, and 50% gave

first-line ratings to pruritus. Clinicians need to ascertain whether these conditions are present and, if they are, they should be addressed regardless of whether antipsychotic drugs or other agents are prescribed for these agitated demented patients.

The first-line recommendation for treating agitated dementia with delusions was an antipsychotic drug alone; the experts would also consider combining a mood stabilizer with an antipsychotic. There was no first-line recommendation for treating agitated dementia without delusions; an antipsychotic alone was a high second-line option (rated first line by 60% of the experts); the experts would also consider a mood stabilizer alone (rated first line by 35%).

Among antipsychotic drugs, the experts recommended risperidone 0.5–2.0 mg/day as the first-line choice for treating agitated dementia. Quetiapine (50–150 mg/day) and olanzapine (5.0–7.5 mg/day) were high second-line options.

It is noteworthy that the survey on which these recommendations were based was completed by the experts at a time when information became available of a potential association between risperidone and cerebrovascular adverse events (CAEs). Specifically, in October 2002, a letter was sent out to physicians in Canada warning about CAEs associated with risperidone. In February 2003, a study by Brodaty et al. found that patients treated with risperidone had more CAEs than patients treated with placebo.²⁵ The investigators reported the following: "Regarding cerebrovascular adverse events, in the risperidone group, 5 patients suffered a stroke and 1 had a transient ischemic attack (TIA). Of these patients, aged between 79 and 89 years, 5 had vascular dementia or mixed Alzheimer's disease (AD)/vascular dementia and 1 had AD. All had medical histories of significant predisposing factors for cerebrovascular events: hypertension (5/6), atrial fibrillation (4/6), and diabetes mellitus (1/6)." In March 2003, the U.S. Food and Drug

Administration (FDA) included the following information in the WARNINGS section of the risperidone package insert:

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73–97) in trials of RISPERDAL in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with RISPERDAL compared to patients treated with placebo. RISPERDAL has not been shown to be safe or effective in the treatment of patients with dementia-related psychosis.

The FDA also included the following information in the ADVERSE REACTIONS section of the risperidone package insert:

Postintroduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL therapy include: ...cerebrovascular disorder, including cerebrovascular accident... A causal relationship with RISPERDAL has not been established.

On April 16, 2003, Janssen Pharmaceutica, L.P., the manufacturer of risperidone, mailed a letter to American physicians informing them of the potential risk for CAEs.

Our methods do not permit us to ascertain to what extent the experts who completed this survey were aware of these findings. However, the survey on which these guidelines are based was sent to experts on February 10, 2003, and all surveys were returned after the Brodaty et al. article was published. Of the 48 surveys, 35 were returned before the date on which the letter from Janssen was mailed to U.S. physicians (23 surveys returned in March 2003 and 12 surveys returned between April 1 and April 16). The remaining 13 surveys were returned in the second half of April 2003 or in May 2003.

We note that, prior to the mailing of the survey, the risperidone label and labels of other atypical and typical antipsychotics already included the same level of warning for various other potential adverse effects, such as neuroleptic malignant syndrome, tardive dyskinesia, and cardiac proarrhythmic effects.

A number of controlled studies have examined the efficacy and safety of risperidone in patients with agitated dementia. Katz et al. reported the first large, double-blind, placebo-controlled study of the efficacy and safety of risperidone in the treatment of psychotic and behavioral symptoms in institutionalized elderly patients with dementia.²⁶ The study involved 625 patients (mean age = 82.7 years) with DSM-IV diagnoses of AD (73%), vascular dementia (15%), or mixed dementia (12%) and significant psychotic and behavioral symptoms; 95% of the patients had severe dementia. Each patient was randomly assigned to receive placebo or 0.5 mg/day, 1 mg/day, or 2 mg/day of risperidone for 12 weeks; 70% of the patients completed the study. Risperidone significantly improved symptoms of psychosis and aggressive behavior in patients with severe dementia.

Risperidone 1 mg/day was found to be the most appropriate dose: it was comparable in efficacy to 2 mg/day and, unlike the 2-mg/day dose, resulted in EPS at a frequency no greater than placebo. In this study, the incidence of CAEs in the group treated with risperidone was similar to that in the placebo group.

The Brodaty et al. study mentioned above was a randomized, double-blind, placebo-controlled trial of the efficacy and safety of risperidone in the treatment of aggression, agitation, and psychosis in 345 elderly nursing-home patients with a DSM-IV diagnosis of AD, vascular dementia, or a combination of the two and significant aggressive behaviors.²⁵ Subjects were randomized to receive 12 weeks of flexible dose treatment with placebo or risperidone solution up to 2 mg/day (mean dose 0.95 ± 0.03 mg/day); 67% of patients in the placebo group and 73% of patients in the risperidone group completed the study. Risperidone was more effective than placebo in reducing aggressive behavior and nonaggressive psychopathology. Overall, 94% and 92% of subjects in the risperidone and placebo groups, respectively, reported at least 1 adverse event. Somnolence and urinary tract infection were more common with risperidone, whereas agitation was more common with placebo. There was a numerical, but not statistically significant, difference in the number of patients who reported EPS between the risperidone (23%) and placebo (16%) groups.

De Deyn et al. compared risperidone, placebo, and haloperidol (tolerability) in the treatment of demented patients with aggression and other behavioral symptoms in a 13-week, double-blind study involving 344 patients.²⁷ Patients were randomly assigned to receive placebo or flexible doses of risperidone (mean dose at endpoint 1.1 mg/day) or haloperidol (mean dose at endpoint 1.2 mg/day). Low-dose risperidone (mean 1.1 mg/day) was well tolerated and associated with reductions in the severity and frequency of behavioral symptoms, particularly aggression, in elderly patients with dementia.

Several studies found olanzapine to be more effective than placebo in the treatment of agitated demented patients. Street et al. assessed the efficacy and safety of olanzapine in treating psychosis and/or agitation/aggression in 206 elderly U.S. nursing home residents with AD in a multicenter, double-blind, placebo-controlled, 6-week study.²⁸ Patients were randomly assigned to placebo or a fixed dose of 5, 10, or 15 mg/day of olanzapine. Low-dose olanzapine (5 and 10 mg/day) was significantly superior to placebo and well tolerated in treating agitation/aggression and psychosis in this population of patients with AD. In a post-hoc analysis of the data from this study, Clark et al. compared the effects of olanzapine and placebo on emergence of hallucinations or delusions in a subset of subjects ($N = 165$) with symptoms of agitation/aggression but little or no psychotic symptomatology at baseline, and found that olanzapine attenuated emergence of psychosis.²⁹ Meehan et al. performed a double-blind study of the efficacy and safety of rapid-acting intramuscular (IM) olanzapine in treating agitation associated with AD and/or vascular dementia and concluded that IM olanzapine may provide substantial benefit in rapidly treating inpatients with

acute dementia-related agitation.³⁰ Note that we did not ask about the use of IM formulations in this survey.

Some studies compared the efficacy and side effects of olanzapine and risperidone in agitated demented elders. In a double-blind study by Fontaine et al., 39 agitated patients with DSM-IV dementia residing in long-term care facilities were administered olanzapine (2.5–10 mg/day, mean dose 6.65 mg/day) ($n = 20$) or risperidone (0.5–2.0 mg/day, mean dose 1.47 mg/day) ($n = 19$). Both drugs produced significant reductions in Clinical Global Impressions scale (CGI) and Neuropsychiatric Inventory (NPI) scores without any statistically significant difference in efficacy.³¹ The chief adverse events were drowsiness and falls. The investigators concluded that low-dose, once-a-day treatment with olanzapine and risperidone are equally safe and effective in treating behavioral disturbances related to dementia in residents of extended care facilities. Martin et al. examined the records of 730 men and women with dementia who had been residents of a skilled nursing facility for at least 90 days to compare the adverse effects of low doses of risperidone ($n = 474$) and olanzapine ($n = 256$).³² Mean dosages of risperidone (0.7–1.0 mg/day) and olanzapine (3.3–4.7 mg/day) were at least 50% lower than the maximum dosages recommended by the Center for Medicare and Medicaid Services for elderly nursing home patients with psychosis or behavioral symptoms of dementia. In this study, falls occurred in 17.9% of patients receiving olanzapine compared with 6.9% receiving risperidone. Laxative use increased significantly more in the olanzapine than the risperidone group.

Note that the experts recommended a dose of 0.5–2.0 mg/day of risperidone and a dose of 5.0–7.5 mg/day of olanzapine for older patients with agitated dementia. This recommendation agrees with the findings concerning optimum dosing in the studies described above.

There is limited literature on use of antipsychotics in dementia with Lewy bodies (DLB). Cummings et al. reported a post hoc analysis of a subgroup of 29 DLB patients included in a larger double-blind, placebo-controlled, randomized parallel group trial of olanzapine for the treatment of psychosis in patients with AD.³³ Of the 29 patients, 10 received placebo, 5 received 5 mg of olanzapine, 7 received 10 mg of olanzapine, and 7 received 15 mg of olanzapine. Results of this preliminary analysis suggested that olanzapine (5 or 10 mg) reduces psychosis in patients with DLB without worsening parkinsonism.

We are aware of three large multicenter, randomized, controlled nursing home trials that have recently been completed. These studies had not been presented or published at the time of our survey of the experts and have still not been published. One is a study of quetiapine versus placebo for treatment of agitation in dementia, and two are studies of aripiprazole versus placebo for treatment of psychosis in dementia.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) for Alzheimer Disease (AD), a multicenter trial developed in collaboration with the National Institute of Mental Health (NIMH), is currently underway to assess the effectiveness of atypical antipsychotics for psychosis and agitation in

outpatients with AD.³⁴ The CATIE for AD is a randomized, parallel group, double-blind study that compares treatment with olanzapine, quetiapine, risperidone, and placebo in AD patients with delusions or hallucinations and/or clinically significant aggression or agitation over 36 weeks of acute treatment, as well as their relative effectiveness in maintaining clinical improvement up to 36 weeks. It is hoped that the CATIE study will provide more definitive answers concerning long-term use of antipsychotics in older patients with dementia. For the moment, clinicians may find additional guidance concerning management of agitation in dementia in other published guidelines.^{9,35}

Schizophrenia. The experts considered delusions, hallucinations, and a long-term history of psychotic symptoms the most important features in diagnosing schizophrenia in an older patient. Other important features were grossly disorganized behavior and disorganized speech. The experts also gave high second-line ratings to symptoms that are useful in distinguishing schizophrenia from delirium, psychosis related to medications or medical illness, and mood disorders.

The experts' first-line recommendation for treating schizophrenia in an older patient was risperidone (1.25–3.5 mg/day). Quetiapine (100–300 mg/day), olanzapine (7.5–15 mg/day), and aripiprazole (15–30 mg/day) were high second-line recommendations. The experts were divided in their ratings of aripiprazole, with 60% giving this agent first-line ratings and 20% third-line ratings, probably reflecting limited experience with this recently introduced agent, which had been approved on November 15, 2002; the survey on which these guidelines were based was completed between March and May 2003. There was limited support for the use of clozapine, ziprasidone, and high-potency conventional antipsychotics.

Available research data on the safety and efficacy of risperidone,^{36–41} quetiapine,^{42–44} and olanzapine^{36,39,45–47} support the experts' endorsement of atypical antipsychotics for the treatment of psychotic disorders in the elderly. It should be noted, however, that nearly all the studies have been open-label and many have only looked at treatment with a single agent.

Arunpongpaisal et al. reviewed all relevant randomized controlled trials that compared atypical antipsychotics with other treatments for elderly patients with a recent (within 5 years) diagnosis of schizophrenia or schizophrenia-like illnesses (e.g., delusional or schizoaffective disorder, schizophreniform psychosis, paraphrenia).⁴⁸ They found no trial-based evidence upon which to base guidelines for the treatment of late-onset schizophrenia, thus highlighting the need for good quality, controlled clinical trials to address the effects of antipsychotic drugs in this group of patients. Until such studies are undertaken, clinicians will need to rely on expert recommendations and clinical judgment in treating patients with late-onset schizophrenia.

In a recent, randomized, multicenter, double-blind trial, Harvey et al. examined the effects of 8 weeks of treatment with risperidone (1–3 mg/day) or olanzapine (5–20 mg/day) on cognitive functioning in 176 elderly patients with schizophrenia or schizoaffective disorder.⁴⁹ The risperidone group had improved

scores on at least one test of attention, memory, executive function, and verbal fluency, and the olanzapine group had improved scores on at least one test of attention and memory function, with no significant differences in change scores between the two groups. The investigators concluded that low doses of risperidone and olanzapine improved cognitive functioning in areas related to functional outcome in elderly patients with schizophrenia or schizoaffective disorder.

Delusional disorder. The experts stressed the importance of accurate differential diagnosis to rule out effects of medications, medical illness, delirium, schizophrenia, and depression. The features the experts considered most important in diagnosing delusional disorder reflect the DSM-IV criteria.

Antipsychotics were the only treatment recommended for delusional disorder. The experts' first-line recommendation for an older patient with delusional disorder was risperidone (0.75–2.5 mg/day), followed by olanzapine (5–10 mg/day) and quetiapine (50–200 mg/day) as high second-line options. There was no consensus on aripiprazole and ziprasidone, while conventional antipsychotics and clozapine were rated third line.

Nonpsychotic major depressive disorder. The experts consider persistent depressed mood, markedly diminished interest or pleasure in activities, and recurrent thoughts of death or suicidal ideation or behavior the three most important discriminating features in diagnosing nonpsychotic major depressive disorder in an older patient. These three symptoms have consistently been endorsed in studies of depression in the elderly and were considered the most important symptoms in diagnosing depression in an older patient by a survey of experts on the treatment of depressive disorders in older patients.¹⁷

The experts' first-line recommendation for agitated nonpsychotic major depression in an older patient was an antidepressant alone (rated first line by 77%), with a selective serotonin reuptake inhibitor (SSRI) the first-line choice, and venlafaxine and mirtazapine high second-line options. There was much less support for tricyclic antidepressants (TCAs), trazodone, and bupropion, while the monoamine oxidase inhibitors (MAOIs) received third-line ratings. Second-line options were an antidepressant plus an antipsychotic (44% first line), electroconvulsive therapy (ECT) (31% first line), an antidepressant plus a benzodiazepine (25% first line), and an antidepressant plus a mood stabilizer (23% first line). Although some clinicians may add antipsychotic drugs on an empirical basis to treat agitated nonpsychotic major depression, there is no clear scientific evidence to support this practice, and only a minority of experts endorsed it. For nonpsychotic major depression accompanied by severe anxiety, the experts again recommended an antidepressant alone (79% first line). They would also consider adding a benzodiazepine to the antidepressant (51% first line) or using ECT (25% first line), but addition of an antipsychotic was clearly not recommended for nonpsychotic major depression with severe anxiety.

We asked the experts about adding an atypical antipsychotic to an antidepressant in an older patient with nonpsychotic

major depression that failed to respond to antidepressants prescribed at adequate dosages and for adequate duration. There was limited support for this strategy; 36% of the experts gave first-line ratings to adding an atypical antipsychotic if a patient had failed adequate trials of two antidepressants.

Psychotic major depressive disorder. To diagnose psychotic major depressive disorder in an older patient, the experts required the presence of both delusions and the following three key depressive symptoms: persistent depressed mood, markedly diminished interest or pleasure in activities, and recurrent thoughts of death or suicidal ideation or behavior (see discussion of nonpsychotic major depressive disorder above).

The treatment of choice for geriatric psychotic major depression was an antipsychotic plus an antidepressant (rated first line by 98% of the experts). ECT was rated first line by 71%. An antidepressant alone or a mood stabilizer plus an antipsychotic received only limited support. Risperidone (0.75–2.25 mg/day) was the first-line option for use in combination with an antidepressant for psychotic major depression (rated first line by 91%). Olanzapine (5–10 mg/day) and quetiapine (50–200 mg/day) were high second-line options (rated first line by approximately 70%). There was no consensus on aripiprazole or ziprasidone.

There is limited literature on the use of antipsychotics in geriatric psychotic depression. Mulsant et al. performed the first randomized study comparing the efficacy of an antidepressant alone (nortriptyline plus placebo) ($n = 14$) or combined with an antipsychotic (nortriptyline plus perphenazine) ($n = 14$) in late-life psychotic depression in 36 patients aged 50 or older.⁵⁰ Both treatments were well tolerated, but rates of response (defined as resolution of both depression and psychosis) did not differ significantly between the two groups (50% for combination treatment vs. 44% for nortriptyline-plus-placebo group).

Mania (bipolar I disorder). The experts considered elevated, expansive, or irritable mood of at least 1 week duration the most important discriminating feature in diagnosing nonpsychotic mania in older patients. Other features the experts endorsed agree closely with the DSM-IV criteria for a manic episode. The two most important diagnostic features for psychotic mania were hallucinations or delusions and elevated, expansive, or irritable mood. The experts endorsed the same additional features as for nonpsychotic mania, but placed more emphasis on ruling out schizophrenia, schizoaffective disorder, and delusional disorder as well the effects of drugs and other substances.

The first-line recommendation for treating mild mania was a mood stabilizer alone. The experts also suggested discontinuing any antidepressant the patient was receiving. For severe nonpsychotic mania, the experts would discontinue any antidepressant and treat the patient with a mood stabilizer plus an antipsychotic. They would also consider a mood stabilizer alone.

For psychotic mania, the treatment of choice was a mood stabilizer plus an antipsychotic (rated first line by 98%). The

experts also recommended discontinuing any antidepressant the patient may be receiving. High second-line options for psychotic mania were ECT, a mood stabilizer plus an antipsychotic plus a benzodiazepine, or an antipsychotic alone. The editors note that one might consider using an antipsychotic alone if there is concern about delirium developing.

There was no first-line recommendation for treating a mixed episode; high second-line options were a mood stabilizer plus an antipsychotic or a mood stabilizer alone.

Risperidone (1.25–3 mg/day) and olanzapine (5–15 mg/day) were the first-line options for use in combination with a mood stabilizer to treat mania with psychosis. Quetiapine (50–250 mg/day) was high second line. Although the experts gave high second-line ratings to combining a mood stabilizer and an antipsychotic in severe nonpsychotic mania, there was less support for specific antipsychotics we asked about in nonpsychotic than in psychotic mania, with risperidone, olanzapine, and quetiapine all rated second line. This probably reflects less support for using an antipsychotic in nonpsychotic than psychotic mania. If it is decided to use an antipsychotic to treat nonpsychotic mania, the experts recommended using slightly lower doses than in psychotic mania.

There are no controlled studies in older patients concerning the use of antipsychotics in combination with mood stabilizers or as monotherapy in the treatment of bipolar disorder.

Other conditions. Specific recommendations concerning the diagnosis and treatment of conditions for which the experts did not recommend antipsychotics are described in Guidelines 9–12 and summarized in the sections that follow.

Panic disorder. The experts considered recurrent unexpected panic attacks (attacks that occur spontaneously “out of the blue”) the most important discriminating feature for geriatric panic disorder. The first-line recommendation for geriatric panic disorder was an antidepressant. High second-line options were cognitive-behavioral therapy (CBT) or an antidepressant plus a benzodiazepine. The experts did not recommend using an antipsychotic in geriatric panic disorder.

Generalized anxiety disorder. The experts considered excessive anxiety and worry that occur more days than not for at least 6 months the most important diagnostic feature for geriatric generalized anxiety disorder. Other diagnostic features were difficulty controlling the anxiety and worry and a feeling of restlessness or being keyed up that accompanies the worry. The experts recommended an antidepressant for the treatment of generalized anxiety disorder (a very high second-line option rated first line by 67%). Other high second-line options were a benzodiazepine, CBT, or an antidepressant plus a benzodiazepine. The experts did not recommend using an antipsychotic to treat geriatric generalized anxiety disorder.

Hypochondriasis. The experts considered fears of having a serious disease that persist despite appropriate medical evaluation and reassurance the most important discriminating feature. The presence of multiple medically confirmed problems in a geriatric patient was not considered important in ruling out the

diagnosis of hypochondriasis. There was no first-line consensus among the experts on the most appropriate treatment for hypochondriasis, perhaps reflecting the paucity of literature in this area. High second-line options were supportive therapy, CBT, or an antidepressant. The experts did not recommend using an antipsychotic to treat hypochondriasis.

Selecting treatments for other indications. The experts did not recommend using an antipsychotic in neuropathic pain, severe nausea and vomiting due to chemotherapy, motion sickness, irritability and hostility in the absence of a major psychiatric syndrome, and insomnia/sleep disturbance in the absence of a major psychiatric syndrome or discrete medical cause. If a patient with neuropathic pain has failed to respond to or tolerate a nonsteroidal anti-inflammatory agent and/or a cyclo-oxygenase-2 inhibitor, the experts would consider an anticonvulsant, with a TCA a high second-line alternative. For severe nausea and vomiting due to chemotherapy, a 5-HT₃ antagonist (e.g., ondansetron or granisetron) was high second line. For motion sickness, the experts preferred an antihistamine such as Dramamine or meclizine and would also consider an anticholinergic agent such as scopolamine. For irritability/hostility in the absence of a major geriatric psychiatric syndrome (dementia, depression, mania, schizophrenia), psychotherapy was rated high second line, followed by treatment with an SSRI, with little support for other medication treatments. For insomnia/sleep disturbance in the absence of a major psychiatric syndrome or discrete medical cause (e.g., sleep apnea, congestive heart failure with nocturnal dyspnea), high second-line options were a hypnotic agent (e.g., zolpidem, zaleplon) or a sedating antidepressant (e.g., trazodone, mirtazapine).

Duration of Treatment

Optimal follow-up intervals. When monitoring elderly patients who are receiving antipsychotics, the experts consider the optimal follow-up intervals to be:

- 1 week after starting an antipsychotic
- 10 days after a change in the dose of the antipsychotic
- 2 months once a patient has been symptomatically stable on the same dose of antipsychotic for 1 month, to monitor for continued therapeutic benefit and tolerability
- 3 months once a patient is in maintenance treatment (i.e., has been stable on the same antipsychotic medication for at least 6 months).

The longest acceptable follow-up intervals for these four situations are 2 weeks, 4 weeks, 3 months, and 6 months, respectively. Note that these intervals are based on the median of the respondents' write-in answers (see Survey Question 37). The authors note that there was a high level of agreement between the psychiatrists and the geriatric internists/family physicians who completed the survey on this question.

Inadequate response. In patients with an inadequate response to an antipsychotic, the experts recommended the following duration of treatment before changing dose or medication:

- Delirium: 1 day (delirium is a medical emergency in which the demands of acute management require frequent reassessment of treatment response and rapid dosage adjustment)
- Dementia with agitation with and without delusions, agitated major depression, psychotic depression, mania with and without psychosis: 5–7 days
- Schizophrenia, delusional disorder: 2 weeks
- Nonpsychotic major depression with severe anxiety: 2 weeks. However, approximately a third of the experts indicated that they would not generally use an antipsychotic to treat nonpsychotic major depression with severe anxiety.

Duration of treatment prior to discontinuation. The experts recommend the following duration of treatment after response before trying to discontinue the antipsychotic:

- Delirium: 1 week
- Agitated dementia with and without delusions: tapering should start in 3–6 months to determine the lowest effective maintenance dose.
- Schizophrenia: indefinitely at the lowest effective dose
- Delusional disorder: 6 months–indefinitely at the lowest effective dose
- Psychotic major depression: 6 months
- Agitated nonpsychotic major depression: 2 months
- Nonpsychotic major depression with severe anxiety: 2 months (Approximately a third of the experts indicated that they would not generally use an antipsychotic to treat nonpsychotic major depression with severe anxiety.)
- Mania with psychosis: 3 months
- Mania without psychosis: 2 months

A retrospective study in a nursing facility described attempts to discontinue or lower the dose of antipsychotic drugs in 75% of subjects and found that residents with appropriate indications for antipsychotic use according to federal regulations were significantly less likely to have their antipsychotic agent stopped.⁵¹ Among those residents whose antipsychotic was discontinued or reduced in dose, in only 20% was the agent subsequently resumed or the dose increased. Recent findings from prospective research suggest that discontinuation of antipsychotic agents is feasible in agitated demented patients who improve after antipsychotic treatment. In a randomized trial of 34 patients with dementia in chronic care institutions, van Reekum et al. investigated the impact of discontinuing long-term antipsychotics.⁵² The patients, who had been on antipsychotics for more than 6 months and whose behavior was stable, were randomized to continue receiving their regular dose of antipsychotics or to receive placebo for 6 months. Although subjects in the active treatment group had significantly more behavioral problems, subjects in the placebo group had a greater tendency (not statistically significant) to be withdrawn from the study as a result of worsening behavior. Nevertheless, early withdrawal from the study was not significantly different between groups. The placebo group developed more apathy, but showed relative improvement in cognitive functioning. Although conclusions are limited by the small sam-

ple size, these findings suggest that a trial of discontinuation of antipsychotics should be considered in this population.

In a randomized double-blind study, Meyers et al. compared the efficacy and safety of continuation combination therapy with nortriptyline-plus-perphenazine to monotherapy with nortriptyline-plus-placebo in 29 older patients with major depression with delusions who had achieved remission after ECT.⁵³ They found that continuation treatment with the conventional antipsychotic perphenazine did not decrease relapse rates but was associated with significant adverse events in older persons after recovery from a delusional depression.

Complicating Conditions That Influence Treatment Selection and Dosing

The experts favored risperidone, with quetiapine high second line, for patients with *cognitive impairment, constipation, diabetes mellitus, diabetic neuropathy, dyslipidemia, xerophthalmia, and xerostomia*. A study of the effects of a single dose of risperidone (0.25 or 0.5 mg), lorazepam (1 mg), or placebo on psychomotor performance and cognitive function in 12 healthy elderly subjects found minor impairment in information processing (digit symbol substitution), motor activity (finger tapping), and postural stability in the risperidone group and greater psychomotor impairment and sedation in the lorazepam group.⁵⁴ Trials comparing cognitive and psychomotor effects of other atypical antipsychotics in older adults with or without dementia are lacking.

The experts would avoid clozapine, olanzapine, and conventional antipsychotics, especially low- and mid-potency agents, in patients with *diabetes, dyslipidemia, or obesity* perhaps because of concerns about elevation of glucose and lipid blood levels and increase in body weight. A U.S. FDA warning issued in October 2003 (after this expert survey study was completed) identified the risk for hyperglycemia and diabetes mellitus as a potential concern for all atypical antipsychotic drugs, although it recognized that this association is not well understood and that the precise risks posed by atypical antipsychotics are not available.⁵⁵ The warning proposed by the FDA recommended that:

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at baseline and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

Risperidone was the experts' first-line choice for patients with diabetes mellitus, with quetiapine and aripiprazole high second-line options. There was no first-line recommendation for obese patients, probably because antipsychotics often lead to weight gain. Risperidone and quetiapine were high second-line options for an obese patient. The experts recommended avoiding clozapine, olanzapine, and mid- or low-potency conventional antipsychotics in obese patients given the propensity of these agents to increase weight. Although there are limited data concerning diabetes in elderly patients, the experts' recommendations reflect findings in the general population suggesting that the atypical antipsychotics are associated with an increased risk of developing diabetes compared with the conventional antipsychotics, and that the risk is highest with olanzapine and clozapine.^{56,57} Studies in younger patients have also found that olanzapine is associated with greater increases in weight, fasting glucose, and lipid levels compared with other atypical antipsychotics.^{58,59} In an open-label study of 180 elderly patients with chronic psychosis, Barak found that risperidone treatment was not associated with weight gain.⁶⁰ Nonetheless, controlled geriatric studies are needed.

The experts preferred quetiapine or olanzapine for patients with prolactin-related disorders such as *galactorrhea* or *gynecomastia*. Pharmacological studies have shown that these drugs cause less prolactin elevation than risperidone.⁶¹

Quetiapine is the first-line recommendation for a patient with Parkinson's disease, perhaps because of its low affinity with the dopamine D₂ receptor; the experts would also consider low-dose olanzapine or clozapine for patients with Parkinson's disease. These recommendations are supported by findings of recent studies of quetiapine and clozapine.⁶²⁻⁶⁸ In a study of 106 patients with Parkinson's disease, Fernandez et al. reported that 87 patients (82%) had partial or complete resolution of their psychosis on quetiapine and that 78 patients remained on quetiapine for a mean duration of 15 months.⁶² In this study, nonresponse to quetiapine and motor worsening were associated with presence of dementia. Morgante et al. compared the efficacy and safety of quetiapine with that of clozapine in 20 parkinsonian patients with dopaminergic psychosis in a 12-week randomized trial.⁶⁴ They found that the patients' psychopathology improved comparably in both treatment groups. There was an improvement in Parkinson's motoric symptoms in the clozapine group while they were unchanged in the quetiapine group. A retrospective review of 43 patients with Parkinson's disease suggested that quetiapine was effective in improving psychosis in approximately 80% of Parkinson's patients both with and without dementia and that patients with dementia were more likely to experience a worsening of motor symptoms.⁶⁶ Another retrospective study documented that 80% of the Parkinson's patients and 90% of the DLB patients had partial to complete resolution of psychosis with quetiapine.⁶⁷ Motor worsening was recorded at some point during quetiapine use in 32% of the Parkinson's patients and 27% of the DLB patients. Although there is a perception among clinicians that psychosis is more difficult to treat in patients with DLB than Parkinson's disease, the investigators

concluded that there was no significant difference in long-term efficacy and motor worsening associated with quetiapine treatment between the two disorders.

The experts did not recommend the use of high doses of risperidone in patients with Parkinson's disease, probably because of concern that it may worsen EPS. Ellis et al. compared the efficacy and safety of risperidone and clozapine in the treatment of psychosis. In a double-blind trial of a small number of patients with Parkinson's disease and psychosis, both risperidone and clozapine were effective in reducing psychopathology but motoric Parkinson's symptoms worsened in some patients treated with risperidone.⁶⁸

Clozapine, ziprasidone, and conventional antipsychotics, especially low- and mid-potency agents, should be avoided in patients with QTc prolongation or congestive heart failure. These recommendations agree with those presented in a detailed review of antipsychotics and their impact on QTc by Glassman et al.⁶⁹ Note that the FDA recently added a black box warning to the labeling of thioridazine concerning the risk of QTc prolongation and torsades de point. Although no cases of torsades de point have been reported with ziprasidone, the labeling for ziprasidone indicates that it should not be used in patients with preexisting QTc prolongation or risk factors for QTc problems (e.g., unstable cardiac disease). Yerrabolu et al. investigated the effect of risperidone on QT dispersion and corrected QT dispersion in a group of elderly patients.⁷⁰ Although risperidone prolonged QT interval, it had no significant effect on QT dispersion, and there were no reports of sudden death or symptoms suggestive of ventricular arrhythmia during this study's follow-up period. The investigators suggested that risperidone can be used safely in elderly patients without risk of increased QT dispersion. This conclusion is supported by the fact that proarrhythmic effects have been reported only at doses that substantially exceed usual therapeutic doses; which, in turn, led to a recent change in labeling for risperidone that suggests QTc prolongation and risk of serious arrhythmia are potential concerns only in overdose situations.

Drug-Drug Interactions

We asked the experts about the appropriateness of combining the different antipsychotics with agents commonly prescribed in older patients; see Survey Question 44 (p. 89). This list of drugs is by no means exhaustive, and older patients may be taking many other types of medications. Clinicians should therefore consult standard tables of drug interactions for more information. We asked the experts to choose between three ratings: 1 = no expected drug interaction; 2 = need for extra monitoring for possible side effects; 3 = combined use contraindicated. Guideline 16 lists only those combinations to which a majority of the experts gave a 2 or a 3, indicating the need at least for extra monitoring when using them.

More than a quarter of the experts considered the following combinations to be contraindicated: clozapine + carbamazepine (rated as contraindicated by 39% of the experts), ziprasidone + TCA (rated as contraindicated by 26%), and a

low-potency conventional antipsychotic + fluoxetine (rated as contraindicated by 27%). Certain combinations of medications caused the experts more concern (e.g., drugs that are potent inhibitors of CYP drug-metabolizing enzymes and thus have increased potential to cause drug-drug interactions).

Antidepressant combinations. The experts had the least concern about combining antipsychotics with citalopram or venlafaxine (all combinations rated a “1” by a majority of the experts). Although we did not ask about escitalopram, one would expect to see the same drug interaction profile as for citalopram. Other antidepressants that were considered fairly safe in combination with most of the antipsychotics were sertraline, bupropion, mirtazapine, and trazodone. The experts were inclined to be much more cautious in combining antipsychotics with the SSRIs that are more potent inhibitors of the CYP 450 enzymes (i.e., fluoxetine, fluvoxamine, and paroxetine) as well as with nefazodone, TCAs, or MAOIs.

Mood stabilizer combinations. The majority of experts recommended extra monitoring when combining any of the antipsychotics with lithium, carbamazepine, lamotrigine, or valproate. An exception was the combination of aripiprazole, risperidone, or a high-potency conventional antipsychotic and valproate, where slightly more than half the experts indicated that no drug interaction would be expected. There was less concern about combining antipsychotics with gabapentin. Note that carbamazepine can reduce plasma levels of aripiprazole by as much as 70%, but this effect of enzyme induction is much less marked with other antipsychotics such as olanzapine.

Other combinations. The experts recommended cautious monitoring when combining any antipsychotic with codeine, phenytoin, or tramadol. With clozapine in particular, the experts recommended cautious monitoring when combining it with nearly all the agents we asked about: atenolol, captopril, digoxin, loratadine, macrolide antibiotics, nifedipine, caffeine, corticosteroids, theophylline, and warfarin. Extra monitoring was also recommended when combining ziprasidone with digoxin, quetiapine with ketoconazole or loratadine, and olanzapine with theophylline. The experts would also provide extra monitoring when combining mid- or low-potency conventional antipsychotics with atenolol, captopril, digoxin, loratadine, macrolide antibiotics, and nifedipine.

Cholinesterase inhibitors. Although we did not ask about combining antipsychotics with cholinesterase inhibitors, these agents are frequently used in older patients with dementia, and a number of studies have looked at these combinations. Zhao et al. performed an open-label, three-way crossover study to determine whether significant drug interactions occur with concomitant administration of donepezil and risperidone.⁷¹ In this study, 24 healthy men were randomly assigned to receive 0.5 mg of risperidone twice daily, 5 mg of donepezil once daily, or both drugs for 14 consecutive days, followed by a 21-day washout

period. No significant pharmacokinetic differences were found between the three groups, and adverse events were minor and comparable in all treatment groups. The investigators noted, however, that further studies are needed to examine the potential for interactions in elderly patients with dementia who may eliminate risperidone and donepezil more slowly and consequently be more vulnerable to drug interactions than the young healthy subjects in this study.⁷¹ Weiser et al. performed a pilot study examining the effects of adding risperidone 0.5–2 mg/day to rivastigmine 3–12 mg/day and vice versa in 65 patients with AD, 10 patients with vascular dementia, and 15 patients with both disorders.⁷² Patients were randomized to open label rivastigmine and risperidone, alone or in combination, for 20 weeks. No clinically relevant adverse interactions were observed in any group. While these preliminary findings suggest that rivastigmine and risperidone can be safely co-administered, large clinical trials are needed to confirm these results.⁷²

SIDE EFFECTS

We asked the experts about choice of antipsychotics for patients with a history of common side effects to antipsychotics. The experts preferred quetiapine for patients with a history of EPS, tardive dyskinesia, or hyperprolactinemia, and would avoid conventional antipsychotics in patients with a history of these conditions. The experts preferred risperidone for patients with excessive daytime sedation and would avoid clozapine and mid- or low-potency conventional antipsychotics in such patients. The experts would avoid conventional antipsychotics and clozapine in patients with a history of central anticholinergic syndrome or significant peripheral anticholinergic syndrome, tachycardia, or drug-induced orthostatic hypotension.

EPS. As noted above, the experts considered quetiapine a first-line option for a patient with a history of EPS; olanzapine and aripiprazole were high second-line options, while the experts would avoid conventional antipsychotics. Findings concerning EPS have been reported in three placebo-controlled studies of risperidone and one of olanzapine in elderly nursing home patients (for a discussion of the efficacy findings in these studies, see the section on Dementia earlier in the introduction). In a 12-week study by Brodaty et al. comparing risperidone (up to a maximum dose of 2 mg/day) and placebo in 345 nursing home patients, there was no significant difference in the number of patients who reported EPS between the risperidone (23%) and placebo (16%) groups.²⁵ In a large, double-blind, placebo-controlled 12-week study of risperidone (at doses of 0.5, 1, or 2 mg/day) in 625 elderly nursing home patients, Katz et al. reported that EPS were among the most common dose-related adverse events, but that the frequency of EPS in patients receiving 1 mg/day of risperidone was not significantly greater than in placebo patients.²⁶ In a 13-week study by De Deyn et al., which compared the tolerability of risperidone (mean dose 1.1 mg/day) and haloperidol (mean dose 1.2 mg/day) with placebo, the severity of EPS with risperidone did not differ significantly

from that with placebo and was less than that with haloperidol.²⁷ In a 6-week, multicenter, double-blind, placebo-controlled study, Street et al. assessed the efficacy and safety of olanzapine (5, 10, or 15 mg/day) in 206 elderly U.S. nursing home residents and reported no increase in EPS at any olanzapine dose relative to placebo.²⁸ Caligiuri et al. examined the incidence of neuroleptic-induced parkinsonism in 56 older, newly medicated, psychiatric patients and found that, even after controlling for spontaneous EPS signs at baseline and their natural fluctuations, there is a substantial risk of EPS in older patients who are treated with very low doses of conventional antipsychotics.⁷³

Tardive dyskinesia. Dolder and Jeste examined the risk of developing tardive dyskinesia in 240 outpatients at least 45 years of age who had borderline tardive dyskinesia at baseline and were treated with conventional or atypical antipsychotics.⁷⁴ They found that patients treated with conventional antipsychotics were approximately two times more likely to develop definitive tardive dyskinesia than those treated with atypical antipsychotics, even though the patients receiving atypical antipsychotics were significantly older and had more severe EPS symptoms at baseline than those receiving conventional antipsychotics. Jeste et al. studied the incidence of tardive dyskinesia in 330 elderly institutionalized patients with dementia treated with risperidone (mean modal dose = 0.96 mg/day).⁷⁵ Although there was no control group, the observed incidence of persistent tardive dyskinesia with risperidone was much lower than with conventional antipsychotics. Jeste et al. compared the 9-month cumulative incidence of tardive dyskinesia in 61 patients treated with risperidone and 61 patients treated with haloperidol (median dose of both drugs = 1.0 mg/day).⁷⁶ The subjects were middle-aged and older (mean age 66 years) and suffered from schizophrenia, dementia, mood disorders, or other conditions with psychotic symptoms or severe behavioral disturbances. Patients treated with haloperidol were significantly more likely to develop tardive dyskinesia than patients treated with risperidone over a 9-month period.

Prolactin concentrations. Kinon et al. examined the effects of antipsychotic treatment on prolactin concentrations in elderly nursing home patients with agitated dementia in whom olanzapine had been newly initiated or who had been switched to olanzapine treatment from either conventional antipsychotics or risperidone.⁶¹ They found that olanzapine appears to be a prolactin-sparing antipsychotic medication in the elderly with only modest prolactin increases observed. In addition, patients who were switched from risperidone to olanzapine experienced a significant reduction in prolactin concentrations. Consistent with these findings, the experts gave high second-line ratings to olanzapine for a patient with a history of hyperprolactinemia.

LIMITATIONS AND ADVANTAGES OF EXPERT CONSENSUS GUIDELINES

These guidelines can be viewed as an expert consultation, to be weighed in conjunction with other information and in the

context of each individual patient-physician relationship. The recommendations do not replace clinical judgment, which must be tailored to the particular needs of each clinical situation. We describe groups of patients and make suggestions intended to apply to the average patient in each group. However, individual patients will differ greatly in their treatment preferences and capacities, history of response to previous treatments, family history of treatment response, and tolerance for different side effects. Therefore, the experts' first-line recommendations certainly will not be appropriate in all circumstances.

We remind readers of several other limitations of these guidelines:

1. The guidelines are based on a synthesis of the opinions of a large group of experts. From question to question, some of the individual experts would differ with the consensus view.
2. We have relied on expert opinion precisely because we are asking crucial questions that are not yet well-answered by the literature. One thing that the history of medicine teaches us is that expert opinion at any given time can be very wrong. For some questions, accumulating research will ultimately reveal better and clearer answers. Clinicians should therefore stay abreast of the literature for developments that would make at least some of our recommendations obsolete. We hope to revise the guidelines periodically based on new research information and on reassessment of expert opinion to keep them up-to-date.
3. The guidelines are financially sponsored by the pharmaceutical industry, which could possibly introduce biases. Because of this, we have made every step in guideline development transparent, reported all results, and taken little or no editorial liberty.
4. These guidelines are comprehensive but not exhaustive; because of the nature of our method, we omit some interesting topics on which we did not query the expert panel.

Despite the limitations, these guidelines represent a significant advance because of their specificity, ease of use, and the credibility that comes from achieving a very high response rate from a large sample of the leading experts in the field.

FINAL WORD

Advances in public health do not always require technological breakthroughs or long periods of waiting for new data. Immediate gains can be made by increasing the speed with which best practices are implemented. Guidelines offer a rapid means for communicating a distillate of expert opinion. When reaching a clinical decision point, practitioners and patients can use guidelines to generate a menu of reasonable choices and then select the option that is judged best for each individual. This process drives the next round of expert opinion and the next round of empirical studies.

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Guideline Organization and Key Terms

Guideline Organization

- I. Indications for Using Antipsychotics in Older Patients
- II. Diagnosis, Medication Selection, and Dosing for Specific Indications
- III. Duration of Treatment
- IV. Complicating Conditions That Influence Treatment Selection and Dosing
- V. Drug-Drug Interactions and Side Effects

Terminology Used in the Ratings

First line is used to designate treatment strategies that came out on top when the experts' responses to the survey were statistically aggregated. These are options that the panel feels are usually appropriate as initial treatments for a given situation. **Treatment of choice** indicates an especially strong first-line recommendation: an option that received the highest rating of "9" (extremely appropriate) from at least 50% of the experts.

Second line is used to indicate treatments that are reasonable choices for patients who cannot tolerate or do not respond to the first-line choices. "High second line" refers to options for which the confidence intervals overlap with the first-line category.

Third line is used to indicate options that are usually inappropriate or used only when preferred alternatives have not been effective.

Definitions of Terms and Assumptions Used in the Survey

Age of Patients. The experts were instructed to assume that the patients asked about in this survey are age 65 years or older.

Antipsychotics. We presented antipsychotics alphabetically within questions and told respondents to opt out of answering

questions about any medication with which they were unfamiliar by drawing a line through that single line item. We asked about the following specific antipsychotics in this survey.

- Conventional Antipsychotics:
 - High-potency (e.g., haloperidol [Haldol], fluphenazine [Prolixin])
 - Mid-potency (e.g., thiothixene [Navane], perphenazine [Trilafon], trifluoperazine [Stelazine])
 - Low-potency (e.g., chlorpromazine [Thorazine], thioridazine [Mellaril])
- Atypical Antipsychotics: aripiprazole (Abilify), clozapine (Clozaril), olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel), ziprasidone (Geodon)

Dosing Levels. In a number of questions, we asked the experts to rate the appropriateness of using different dose levels of antipsychotics in a variety of clinical situations. In considering the dose level they would use for each antipsychotic, the experts were told to think of the following doses of risperidone as an example.

- Low dose: < 0.75 mg of risperidone
- Medium dose: 0.75–1.25 mg of risperidone
- High dose: > 1.25 mg of risperidone

Additional Instructions. Our intention in this survey was to identify what experts believe is the optimal treatment strategy in a variety of situations. The experts were instructed to answer only those questions for which they either knew the literature well or had sufficient clinical experience. If they were unfamiliar with a specific condition or treatment, they were instructed to skip the question or option and draw a line through it. In some cases, we asked about treatments that would not usually be considered appropriate. Negative ratings are very valuable in guiding physicians concerning treatments to be avoided.