Commentary

Expert Consensus Guidelines for Using Antipsychotic Agents in Older Patients

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In the United States, there are about 2600 board-certified geriatric psychiatrists but over 35 million elderly people. Thus, many elderly patients with psychiatric conditions are treated solely by primary care physicians or general psychiatrists, some of whom may not have received training sufficient for addressing the needs of the elderly population. Although randomized clinical trials remain the gold standard upon which to base clinical guidelines, these trials do not cover all aspects of clinical practice that physicians may face.

The goal of the *Expert Consensus Guidelines: Using Antipsychotic Agents in Older Patients* is to answer clinical questions that are not adequately addressed by research on the use of antipsychotics in older patients. The survey on which these *Guidelines* are based had 3 main goals: (1) to identify geriatric disorders for which antipsychotic treatment is inappropriate because of the increased risk of undesirable side effects or a lack of any clear therapeutic benefit; (2) to identify the indications for antipsychotics in the elderly, as well as appropriate dosages and duration of treatment; and (3) to determine under what conditions (i.e., comorbid disorders, concomitant medications) disease-drug and drug-drug interactions are most likely to occur with antipsychotic treatment. The survey on which the *Guidelines* are based was completed by 48 leading experts in the field of geriatrics (geriatric psychiatrists and geriatric internists/family physicians) who were asked about current best clinical practice. This commentary highlights selected important results of the survey.

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WHEN ANTIPSYCHOTICS SHOULD NOT BE USED IN THE ELDERLY

The experts' responses indicated that antipsychotic agents should not be used to treat generalized anxiety disorder, panic disorder, hypochondriasis, nonpsychotic major depression even in the presence of severe anxiety, insomnia or other sleep disturbances, irritability and hostility in the absence of a major psychiatric syndrome, motion sickness, neuropathic pain, and severe nausea and vomiting (e.g., due to chemotherapy) (Guideline 1). The reasons for this opinion may include an unfavorable risk-benefit ratio; that is, antipsychotic agents are not particularly effective in these conditions, and their low potential for therapeutic benefits usually does not justify the high risk of side effects in older patients.

APPROPRIATE USE OF ANTIPSYCHOTICS IN THE ELDERLY

Delirium

Short-term use of antipsychotics was recommended as a symptomatic treatment for delirium, concurrent with specific treatment of the underlying condition, e.g., drug toxicity, dehydration or other metabolic abnormalities, or infection. There was no consensus among the experts on a first-line antipsychotic drug for delirium. Risperidone, 0.75 to 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. Haloperidol is often used in patients who are unable to receive oral medication.

Treatment of Agitated Demented Patients

Antipsychotic monotherapy was strongly recommended as a first-line treatment (Guideline 3B) for agitated dementia or delusions. The combination of a mood stabilizer plus an antipsychotic was also recommended as a high second-line choice. However, antipsychotics were not as strongly favored in the treatment of agitated dementia *without* delusions. Whereas 94% of experts

listed antipsychotics as the first-line treatment in dementia with agitation and delusions, only 60% of experts listed antipsychotics as a first-line treatment in dementia with agitation without delusions (Survey Questions 11 and 12). In fact, there was no first-line recommendation for dementia with agitation without delusions, which probably reflects the opinion that a highly effective drug treatment has yet to be found. The target doses of antipsychotics for agitated dementia syndromes were risperidone, 0.5 to 2.0 mg/day; quetiapine, 50 to 150 mg/day; and olanzapine, 5 to 7.5 mg/day.

Schizophrenia

Antipsychotics are the first-line treatment for late-life schizophrenia. Atypical antipsychotics were favored over conventional antipsychotics. Approximately 93% of the experts rated risperidone as first-line treatment for geriatric schizophrenia, while 67% of experts rated quetiapine or olanzapine as first-line, and 60% rated aripiprazole as first-line (Survey Question 20). The target doses for antipsychotics were higher for older patients with schizophrenia than for older patients with other psychiatric disorders. For example, the mean target dose of risperidone was 2.4 mg/day for schizophrenia compared with 1.6 mg/day for delusional disorder (Survey Questions 20 and 25).

Mood Disorders

A combination of an antidepressant and an antipsychotic was recommended as treatment of choice (rated first-line by 98% of the experts) for psychotic major depression (Guideline 7B). Antipsychotics were not favored in the treatment of nonpsychotic major depression even in the presence of severe anxiety. In nonpsychotic geriatric depression, the experts recommended the use of antidepressants alone (Guideline 6B). Among the antidepressants, newer agents, such as selective serotonin reuptake inhibitors (SSRIs), venlafaxine, and mirtazapine, were favored (Guideline 6C).

Antipsychotics were not recommended in mild mania, although the experts considered the combination of a mood stabilizer and an antipsychotic to be the treatment of choice for psychotic mania and would consider antipsychotics as an adjunctive treatment in severe nonpsychotic mania (Guideline 8C).

TRIAL DURATION AND FOLLOW-UP

Clinical trials seldom address questions concerning the duration of treatment with antipsychotic agents. For example, at one end of the spectrum is delirium, for which experts recommended a treatment duration of about 1 week after response; at the other end of the spectrum is schizophrenia, which is often a lifelong illness requiring indefinite treatment (Guideline 14). It is important to note that Omnibus Budget Reconciliation Act regulations for long-term care facilities specify that an attempt should be made to taper or discontinue antipsychotic drugs at least every 6 months, with a provision that, if 2 trials of tapering have failed and the patient has relapsed, another attempt to taper may be considered "clinically contraindicated." However, these regulations do not make a distinction depending on the indication for which the antipsychotic is being prescribed (e.g., for delirium or dementia or schizophrenia). In contrast, the *Expert Consensus Guidelines* provide specific guidance about duration of treatment according to the type of condition. The experts' recommendations may be used by health care policy makers who are trying to improve the quality of care in long-term care facilities.

Randomized controlled trials are not informative in defining appropriate intervals for follow-up care when prescribing antipsychotic drugs (Guideline 13). This is an important area because insurers often impose guidelines and restrictions on the frequency of covered visits. The *Expert Consensus Guidelines* provide guidance to practitioners concerning both optimal and minimal acceptable intervals for follow-up after initiating, titrating the dose of, or stabilizing a patient with an antipsychotic agent. These recommendations will not only be useful for practitioners in clinical decision making, but may play a role in guiding the development of health care policy and regulatory standards.

SPECIAL ISSUES IN USING ANTIPSYCHOTICS IN THE ELDERLY

Since elderly patients experience more medical problems than younger patients and may be receiving multiple medications, there is increased concern about the potential for disease-drug and drug-drug interactions when treating older patients with antipsychotic agents. These issues must often be addressed in health care settings, including many HMOs and nursing homes, that have restricted formularies. Formulary decisions in such settings are often based on cost when drugs of comparable efficacy are available. As a consequence of financial incentives and formulary restrictions, conventional antipsychotics may be more likely to be prescribed in these settings than atypical antipsychotics. With geriatric populations, however, it is especially important to consider safety and tolerability along with efficacy and cost. For example, the experts recommend that low- and mid-potency conventional antipsychotic drugs, as well as clozapine and ziprasidone, should be avoided in the treatment of elderly patients who have corrected QT interval (QTc) prolongation (Survey Questions 42 and 43). In terms of formulary policy, it is important that older adults and their physicians be able to select from a wide range of medications, so that pharmacokinetic and side effect profiles can be matched to the individual patient's medical conditions and concurrent medication profile, in order to minimize the potential for adverse

effects. This option may become an issue with the implementation of Medicare prescription drug coverage. The responses to this survey study suggest that the experts have specific concerns about disease-drug and drug-drug interactions.

Disease-Drug Interactions

Antipsychotic use has been associated with the onset and worsening of several diseases. These specific concerns are reflected in the experts' responses to Survey Questions 42 and 43, in which the experts rated the appropriateness of the different antipsychotics for use in patients with a variety of complicating medical conditions. The experts indicated the importance of avoiding low- and mid-potency conventional antipsychotics, clozapine, and olanzapine in patients who have diabetes mellitus, dyslipidemias, and/or obesity. Another area of particular concern in the elderly is related to prolongation of QTc and congestive heart failure. The experts would avoid (gave third-line ratings to) ziprasidone, low- and mid-potency conventional antipsychotics, and clozapine in patients who have a prolonged QTc interval or congestive heart failure. Quetiapine is the first-line recommendation for a patient with Parkinson's disease, perhaps because of its low affinity with the dopamine D_2 receptor; the experts would also consider low-dose olanzapine or clozapine for patients with Parkinson's. The experts did not recommend the use of high doses of risperidone in patients with Parkinson's disease, probably because of concern about worsening extrapyramidal symptoms.

Drug-Drug Interactions

We asked the experts about potential problems (drug-drug interactions) that could arise in combining antipsychotics with a wide range of agents that are commonly used by older patients. The experts' responses reflect concern about interactions related to drug metabolism, specifically the concomitant use of drugs that have potent inhibitory effects on cytochrome P450 enzymes (Survey Question 44).

The experts recommended avoiding or being very cautious in using the following 3 combinations: clozapine and carbamazepine; ziprasidone and a tricyclic antidepressant; and a low-potency conventional antipsychotic and fluoxetine. These combinations were rated as contraindicated by more than 25% of the experts. There were also concerns about combining antipsychotics with the SSRIs that are potent inhibitors of the cytochrome P450 enzymes, e.g., fluoxetine, fluvoxamine, and paroxetine, as well as with nefazodone, tricyclic antidepressants, and monoamine oxidase inhibitors. For example, 69% of the experts recommended extra monitoring when combining clozapine with fluoxetine, since fluoxetine inhibits the enzymes that are required for metabolizing clozapine. Extra monitoring was also recommended when combining antipsychotics with mood stabilizers, such as lithium, carbamazepine, lamotrigine, or valproate. 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. Approximately 50% of the experts did not recommend extra monitoring when combining aripiprazole, risperidone, or high-potency conventional antipsychotics with valproate. Extra monitoring was also recommended when combining antipsychotics with the narcotics codeine and tramadol.

In summary, the potential for drug-drug interactions when combining antipsychotics with other agents is substantial, but the specific types of interactions cannot easily be committed to memory by the busy practitioner, and new information on potential enzymatic effects and drug interactions is emerging. The list of drugs covered by this survey study is by no means exhaustive, and older patients may be taking many other types of medications. It is, therefore, important for clinicians to make a regular practice of checking up-to-date tables of potential drug-drug interactions or consulting with pharmacists who can check the existing databases on potential drug-drug interactions to be sure that combinations are sufficiently safe.

SUMMARY

With increasing numbers of primary care physicians prescribing antipsychotic treatment for elderly patients, it is essential that up-to-date and accurate information be accessible to all physicians concerning the appropriate use of these agents. Practitioners need to know when antipsychotic treatment is necessary and appropriate, what doses to use, and for how long treatment is necessary. Although the "gold standard" in the field remains practice guidelines based on evidence from randomized clinical trials, we recognize that it is not possible for clinical trials to answer all of the questions that practitioners face in everyday decision making regarding the care of individual patients. These *Expert Consensus Guidelines* are designed to help answer some of those questions and provide guidance concerning selection of specific agents, dosing, length of treatment, and treatment discontinuation. The survey responses that were used to develop these guidelines are based on current practice and available scientific information. However, research in this area is ongoing, and these guidelines may need to be updated or revised as more information from ongoing and future clinical trials becomes available.