Adverse Reactions of Antidepressants in Elderly Patients

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As patients age, adverse drug reactions increase dramatically in frequency and severity. Although the population of elderly patients in controlled studies of antidepressants is small, key factors have been identified that may influence proper dosing, including the different pharmacokinetic properties of antidepressants in elderly compared with younger patients and individual patient characteristics. In elderly patients, antidepressant side effects of concern include orthostatic hypotension, anticholinergic effects, extrapyramidal symptoms, and syndrome of inappropriate antidiuretic hormone secretion. A routine treatment procedure that includes risk-factor identification, a thorough drug history, patient and caregiver education on compliance, and use of the lowest effective dose can help clinicians effectively manage elderly patients and limit the risk of adverse drug reactions.

(J Clin Psychiatry 1999;60[suppl 20]:4–8)

The incidence and severity of adverse drug reactions (ADRs) increase with age. ADRs of all types are 7 times more frequent in those aged 70 to 79 years than in those aged 20 to 29 years. Overall, one sixth of all hospital admissions of patients over the age of 70 years have been attributed to ADRs, in contrast to only 1 in 35 admissions for the rest of the population.[1] Precise estimates of ADRs specifically due to psychotropic drugs and antidepressants are lacking. Nonetheless, psychotropics figure prominently, with cardiovascular medications and nonsteroidal anti-inflammatory drugs, as a common cause of drug-related problems in the elderly.

A continuing challenge is to disentangle whether the increase in ADRs with aging is due to age-associated physiologic changes as opposed to specific medical comorbidities and specific drug-drug interactions.[2,3] As many as 20% of those older than 65 years of age have multiple health problems and thus require substantial medical treatment.[4,5] The average older American uses 3 prescription drugs and 4 over-the-counter medications daily,[6] whereas the typical nursing home resident takes 7 different prescription medications per day.[7] Although those older than 65 years represent 13% of the U.S. population, they consume up to 35% of all prescription drugs.[8] However, not all of these prescriptions are appropriate,[9] which may lead to an increase in the rate of ADRs and drug-drug interactions.

In addition, noncompliance by the patient also contributes to ADRs. Noncompliance is intensified in the elderly by the complexity of the medication regimens inherent to their multiple illnesses and is further complicated by communication difficulties arising from impaired hearing, cognitive impairment, and language and cultural differences.[10]

SHORTCOMINGS OF DRUG TRIALS

Until recently, older subjects, especially those with multiple medical problems, were systematically excluded from clinical drug trials. A review by Salzman and colleagues of English-language publications of any type, including case reports, that were relevant to treatment of late-life depression identified only 171 patients who were older than age 75.[11] Data on the efficacy and safety of antidepressant medications in the elderly, particularly the "old-old" (those older than age 75 years), remain relatively scant.[12] Nonetheless, in the past few years, the generally more favorable side effect profiles of newer medications[13] have permitted a noticeable shift in clinical research toward treatment trials in higher risk populations (i.e., those with comorbid medical conditions, the old-old, and residents of long-term care facilities), as evident by Dr. Carl Salzman's article in this supplement. Moreover, maintenance antidepressant treatment in geriatric depression is now a subject of active investigation, as exemplified by the work by Dr. Charles F. Reynolds, III, and colleagues (article by Walters et al., this supplement). This avenue of research is important because of the high preva-

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Presented at the closed roundtable "Treatment of Depression in Long-Term Care Patients," Sept. 18–19, 1998, Boston, Mass. This roundtable was supported by SmithKline Beecham Pharmaceuticals.

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lence of depression in elderly patients, as documented by Drs. Benoit H. Mulsant and Mary Ganguli (this supplement), and the need to improve the recognition and treatment of the condition, particularly in the primary care setting, as explained in Dr. C. Brendan Montano's article (this supplement).

An additional limitation in traditional regulatory drug trials is that the new entity is usually not contrasted with a currently recommended treatment standard.[14] For example, amitriptyline, which is not considered the antidepressant of choice in older adults, is often compared with newer agents in medication trials. Thus, the study reported in the article by Dr. Steven P. Roose and Erica Spatz (this supplement) is important, not only for its implications for the treatment of depressed patients with comorbid ischemic heart disease, but also because it represents the first comparative trial of a selective serotonin reuptake inhibitor (SSRI)—paroxetine—with our prior gold standard for cardiac and older patients with depression, plasma level–monitored nortriptyline.[15]

SPECIAL CONSIDERATIONS IN THE ELDERLY

In this supplement, Dr. C. Lindsay DeVane and I review pharmacokinetic changes that may be pertinent to antidepressant therapy in the elderly. This is examined in terms of cytochrome P450 isoenzyme–specific metabolism, which also has important implications for containing drug interactions in long-term care patients.[16] Although elderly patients frequently require lower doses of medications, age alone does not indicate the need for dosage modification. More importantly, it is necessary to consider individual patient characteristics, such as cardiovascular or renal function, genetic and acquired differences in body composition, and drug metabolism, together with a drug's physicochemical properties when determining proper dosing.[2]

Underlying differences among patients related to age or illness require careful consideration with regard to pharmacotherapy. As patients age, there is a general reduction in homeostatic mechanisms (e.g., postural control, orthostatic circulatory responses, thermoregulation, visceral muscle function, laryngeal reflexes, hypoxic responses, and cognitive function). This may interfere with the ability to adapt to changes in the environment and may be manifest as ADRs. In addition, active metabolites of some antidepressants may accumulate in aged patients.[17]

Adverse Drug Reactions

When the tricyclic antidepressants (TCAs) were the most efficacious antidepressants available, clinicians recognized that the elderly were especially sensitive to their adverse effects. In particular, the cardiac and cognitive sequelae associated with TCA use were especially problematic. Dr. Stephen P. Roose and Erica Spatz and Dr. Robert D. Nebes and coworkers, respectively, review their recent data addressing these concerns (this supplement). A number of additional complications are common and also worth mentioning: the risk of hip fractures, the anticholinergicity of antidepressants, and 2 more recently recognized SSRI-related ADRs of concern in long-term care patients, extrapyramidal side effects and inappropriate antidiuretic hormone secretion.

Hip fracture. Falls with the concomitant risk of hip fracture are of grave concern in the frail elderly. Given the effects of TCAs and monoamine oxidase inhibitors on orthostatic blood pressure, it is not surprising that antidepressants figured prominently in epidemiologic studies of this risk.[18] What is surprising is that the SSRIs as a class do not appear to have diminished this risk.[19,20] The risk of hip fracture appears greatest shortly after initiation of antidepressant therapy and declines over time.[20] Laghrissi-Thode and colleagues reported results from 2 studies that compared the effects of an SSRI and nortriptyline on body sway. The earlier study reported a significant increase in body sway compared with baseline among patients receiving sertraline (N = 10) after 1 week of therapy.[21] In the second week of therapy, the change in body sway was not significant. The second study, with paroxetine, found that this SSRI had no significant effect on body sway compared with baseline.[22] Similar results were reported for patients who received nortriptyline in this study. The first study with sertraline requires replication in a larger study conducted under double-blind conditions, as was done with the comparison study of nortriptyline and paroxetine.

In contrast to concerns about hypotension with older antidepressants, slight increases in blood pressure have been documented with venlafaxine, particularly in patients taking higher doses of the drug.[23–25]

Anticholinergic effects. A second traditional concern with the use of antidepressants in long-term care patients, particularly with the older TCAs, is the consequences of their atropinic effects. Anticholinergic effects may arise from either those medications used therapeutically for their anticholinergic properties (e.g., oxybutynin, benztropine) or those that have anticholinergic effects that are incidental to their main actions (e.g., amitriptyline). Peripheral manifestations of anticholinergicity include dry mouth, tachycardia, blurring of vision, urinary retention, and constipation. Common difficulties in older patients, such as constipation, xerostomia, glaucoma, and urinary retention, may be markedly exacerbated by even modestly anticholinergic medications. In addition, tachycardia in patients with preexisting myocardial ischemia is of particular concern since these effects do not appear to be ameliorated by time. Anticholinergic effects on the central nervous system may range from subtle changes, such as apparent worsening of depression, mild confusion, and impairment of recent memory, to frank delirium. The total anticholinergic burden of medication has been quantified

by measuring serum anticholinergicity (SA), which has been associated with delirium, as well as more subtle impairments in memory, attention, and self-care capacity. Cognitive impairment secondary to medications may be especially relevant for those patients with comorbid depression and dementia.

The SSRIs have greatly advanced the pharmacotherapy of late-life depression by their apparent absence of antimuscarinic effects, although these effects may still occur with use of newer antidepressants.[26] In vitro radioreceptor data that show paroxetine to be a more potent muscarinic antagonist than nortriptyline have not, however, been consistent with our clinical experience. Consequently, we compared anticholinergicity, in sera, obtained from older patients treated with paroxetine and nortriptyline. We recently reported a study of 61 patients with a mean ± SD age of 73.2 ± 7.5 years (range, 60.4–95.1 years) who had been randomly assigned to double-blind treatment with either nortriptyline (target plasma level of 100 ng/mL) or paroxetine (20 mg/day, or 30 mg/day if minimal response after 2 weeks).[3] Prior to treatment, there were no significant differences between drug-treatment groups in demographic or clinical characteristics or medical burden. The changes from baseline in SA after 1, 4, and 6 weeks of treatment were significantly greater for the nortriptyline-treated patients compared with the paroxetine group at all times (Table 1).

In contrast to in vitro results, our findings in older patients suggest that at therapeutic doses, paroxetine has approximately one fifth the anticholinergic potential of nortriptyline. It should also be noted that the significant correlation of plasma nortriptyline concentrations with SA suggests a dose-response relationship that was not apparent for paroxetine.

Reasons for the apparent discrepancy between in vitro and in vivo results are not certain, but may be partially explained by the contributions of the hydroxylated metabolites of nortriptyline. In our study, these metabolites were present in greater concentrations than nortriptyline. The hydroxylated metabolites of nortriptyline are known to be substantially less protein bound than their parent, to possess anticholinergic activity, and to substantially increase in older patients because of diminished renal clearance.[27] In contrast, paroxetine does not appear to have active metabolites with anticholinergic potential. It is also possible that the mild anticholinergic effect of paroxetine is helpful in avoiding diarrhea, gastrointestinal disturbances, and extrapyramidal side effects, which have been noted to be more prominent in older patients taking sertraline or fluoxetine.[28]

Extrapyramidal symptoms. Drug-induced parkinsonism, including dystonic reactions and akathisia, as well as worsening of motor disability in patients suffering from idiopathic Parkinson's disease have been reported in older patients treated with SSRIs.[29,30] These data are limited, however, since they are based on case reports and since SSRI treatment occurred in the presence of concomitant medication that can contribute to extrapyramidal symptoms (EPS).[31] This effect is perhaps the consequence of both age-associated reductions in dopaminergic function[32] as well as serotonergic effects on dopamine outflow.[33,34] Most reports of EPS in the literature are associated with fluoxetine, which may be due to the fact that this SSRI was the first to reach the market. One study of a database of 5555 patients found 15 cases of EPS related to fluoxetine over a 4-year period, 7 of which involved fluoxetine as the only psychotropic medication.[35] The events were not dose related. Sertraline therapy appears to be associated with a lower risk of EPS than fluoxetine,[31] although at least 2 case studies show that EPS may occur in patients receiving sertraline as well.[36,37]

Table 1. Change in Baseline Serum Anticholinergicity in Patients Treated With Nortriptyline or Paroxetine[a]

	Nortriptyline N = 30			Paroxetine N = 31				
Week	N	Mean	SD	N	Mean	SD	z	p Value
Week 1	29	0.35	0.48	31	–0.02	0.14	4.15	.0001
Week 4	20	0.34	0.37	24	0.06	0.30	3.55	.0004
Week 6	22	0.30	0.36	22	0.07	0.27	2.57	.0101

[a]Data from reference 3.

We recently compared the change from baseline EPS using an objective rating scale before and after treatment with either paroxetine or nortriptyline in a double-blind study of elderly patients with depression. Forty subjects randomly assigned to either paroxetine or nortriptyline treatment were assessed for EPS before treatment and after 6 weeks of antidepressant medication using the UKU Side Effect Rating Scale.[38] The 2 groups did not differ in baseline demographic characteristics, clinical measures, or baseline UKU ratings for dystonia, rigidity, hypokinesia, hyperkinesia, tremor, and akathisia. Mild baseline EPS were present in both groups. Both groups showed an improvement in all EPS following 6 weeks of antidepressant treatment.[39] Paroxetine and nortriptyline treatment reduced EPS measures in elderly depressed subjects. Similar studies with other SSRIs are needed. In general, the positives of SSRI therapy far outweigh the potential for EPS, even in patients such as the elderly who are at greater risk for movement disorders.[31]

Syndrome of inappropriate antidiuretic hormone secretion. In older patients, antidepressants, including TCAs and SSRIs, have been associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). While SIADH is a rare adverse effect of many psychotropic medications, the majority of reports of antidepressant-induced SIADH have involved patients older than 65 years and have implicated fluoxetine, although there are reported cases with newer antidepressants, such as venlafaxine and nefazodone.[40–43] In an analysis of 760 reports of

hyponatremia associated with SSRIs, the median time to onset of the hyponatremia was 13 days (range, 3–120 days).[44] Only about 30% of patients presented with hyponatremia more than 3 months after initiation of SSRI therapy.

According to a review by Sharma and Pompei, exactly how antidepressants may interfere with water and salt metabolism to cause hyponatremia is unknown, but at least 2 hypotheses exist to explain this mechanism.[45] First, the development of dry mouth as one of the side effects associated with many antidepressants may prompt an increase in water intake. Another potential explanation is that catecholamine activity encourages the release of antidiuretic hormone (ADH), as occurs when a TCA blocks the reuptake of catecholamines. The rate of water intake rather than the degree of ADH release has been shown to affect the severity of SIADH.[46]

Even mild SIADH can lead to significant water retention and central nervous system effects; thus, it is important to be vigilant for symptoms of rapid weight gain, lethargy, weakness, and early delirium when initiating an SSRI in an older patient. In these circumstances, the physician should have a low threshold for checking serum sodium, because if this measure is borderline, the patient may be responsive to fluid restriction. Hyponatremia can have serious neurologic effects, including morbidity, so physicians must be attentive to the early clinical manifestations of hyponatremia, which include lethargy, disorientation, and muscle cramps. The condition should be suspected in all SSRI patients whose condition deteriorates, and a confirmation of the diagnosis can be accomplished by periodically monitoring serum electrolytes. Discontinuation of all medications that may cause an imbalance in salt and water clearance is a key step in managing the condition.[45] Mild cases can usually be treated with fluid restriction, while severe cases may require hypertonic saline. When the offending cause is an antidepressant, the antidepressant may be started at a lower dose or another antidepressant may be used once the hyponatremia is brought under control.

Although all of these unanticipated effects have now been reported with other SSRIs, it is not possible, at present, to determine the differential geriatric side effect profile of the more recently introduced medications, given the much longer and more extensive use of fluoxetine in the United States and the lack of comparative trials. A particular concern, however, with the use of fluoxetine is that should SIADH appear, it may take several weeks to ameliorate after discontinuation of fluoxetine.[47]

RECOMMENDATIONS FOR PRACTICE

As patients age, pharmacodynamic changes and concomitant illness will significantly alter their response to medication. Psychiatrists treating older patients should employ a set of routine procedures, as follows: (1) Identify patient risk factors such as medical status and use of high-risk medications (i.e., anticoagulants, antihypertensives, and antiarrhythmics); (2) Take a thorough drug history, involving caregivers and relatives, that includes over-the-counter medications and make regular updates in a prominent place in the patient's record; (3) Educate patients and caregivers about the prescribed medications and their dosing regimens and monitor compliance; (4) Use the lowest effective doses and avoid unnecessary polypharmacy, but don't undertreat; (5) If there is a deterioration in patients' physical or cognitive state, always suspect an ADR.

Drug names: amitriptyline (Elavil and others), benztropine (Cogentin and others), fluoxetine (Prozac), nefazodone (Serzone), nortriptyline (Pamelor and others), oxybutynin (Ditropan and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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