Management Considerations for Late-Life Depression

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The prescribing of antidepressants for patients with late-life depression is complicated by a number of factors related to the aging process. As a result of age-related changes in brain neurotransmitters and receptors, elderly patients are generally more sensitive to both the therapeutic and toxic effects of drugs. Drug pharmacokinetics are also altered in the elderly, causing accumulation and reduced clearance and generally necessitating the administration of lower doses than in younger patients. Elderly patients frequently require treatment with multiple drugs owing to concomitant illness, increasing the possibility of drug interactions and causing compliance difficulties. In general, antidepressants should initially be prescribed at a low dose, and then the dose should be increased slowly, if necessary. Since prolonged maintenance therapy is required to prevent relapse or recurrence of depression, tolerability and compliance are also important issues affecting drug choice in elderly patients.

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The prescribing of antidepressants for patients with late-life depression is complicated by a number of factors related to the aging process. These include pharmacodynamic changes, altered drug pharmacokinetics, and polypharmacy. Additional considerations are the duration of antidepressant therapy and the need for maintenance therapy. This article presents an overview of management issues in late-life depression.

PHARMACODYNAMIC CHANGES IN THE ELDERLY

The normal aging process is associated with changes in receptor density and brain neurotransmitter levels, both of which can alter the pharmacodynamics of antidepressant drugs. In general, as a consequence of these changes, elderly patients become more sensitive to both the therapeutic and toxic effects of drugs.

Four specific neurotransmitter systems are of clinical significance when prescribing antidepressant therapy: cholinergic, dopaminergic, adrenergic, and serotonergic. Age-related changes in these neurotransmitters have been well studied. A decline in brain levels of the neurotransmitter acetylcholine causes elderly patients, in particular the very old, to become exceptionally sensitive to drugs with anticholinergic properties, such as the tricyclic antidepressants (TCAs).[1] Central dopamine levels, also reduced in old age, place elderly patients receiving dopaminergic antagonists at increased risk of extrapyramidal side effects; this is a particular problem with neuroleptic drugs.[1] Alterations in the noradrenergic and serotonergic neurotransmitter systems may increase the sensitivity of patients to antidepressant drugs. In addition, a reduction in the sensitivity of α_1-adrenoceptors has been documented in elderly patients, resulting in an increased proclivity toward orthostatic hypotension during treatment with TCAs.[2] This is compounded by a decrease in the density of central baroreceptors. Changes in histamine H_1 receptor density may increase the sensitivity of elderly patients to the sedative properties of TCAs.

PHARMACOKINETIC CHANGES IN THE ELDERLY

Aging results in many physiologic changes that can alter drug pharmacokinetics. Antidepressant drugs, which are lipid-soluble molecules, may have a larger volume of distribution in elderly subjects than in younger patients owing to an increase in body fat that occurs with old age.[3] Drug clearance is also impaired, causing drug accumulation, increased blood levels, and, possibly with time, drug toxicity.[3] For example, citalopram is reported to reach up to 4 times greater steady-state plasma levels in elderly subjects than would otherwise be expected following 20-mg/day dosing.[4] In general, the elderly tend to have higher blood drug levels at any given dose than younger patients. As a consequence of the combined effects of aging on drug disposition and sensitivity, the majority of older patients need lower drug doses than those recom-

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mended for younger patients. However, the elderly population does exhibit considerable heterogeneity, and some of these patients may require similar or even higher doses than younger patients. For example, some patients over the age of 75 years exhibit decreased sensitivity to the effects of desipramine.[5]

THE EFFECT OF POLYPHARMACY ON ANTIDEPRESSANT PRESCRIBING

Elderly patients tend to suffer from multiple diseases that are often chronic in nature. Consequently, they tend to receive concurrent treatment with several drugs. Studies of polypharmacy in the elderly population suggest that as a group, the elderly take more drugs at the same time than younger patients. Overall, elderly patients receive between 2 and 18 different drugs concomitantly, with the number of drugs correlating with the patient's age, degree of infirmity, and living situation.[6] Patients in general hospitals receive a mean of 6.5 drugs simultaneously, whereas those in psychiatric hospitals and nursing homes receive even higher numbers of concomitant drugs.[6] Interestingly, of the drugs taken by the elderly, one third are prescribed to counteract the side effects of other drug therapy.[6]

Polypharmacy in the elderly has 2 major implications with respect to prescribing therapy for late-life depression. First, the potential for clinically meaningful drug interactions is increased, and second, patient compliance may be adversely affected.

Drug Interactions

Psychotropic drugs interact with a variety of other medications. For example, water-soluble potential cardiotoxic hydroxymetabolites of TCAs are eliminated renally and may accumulate in the presence of antibiotics such as the tetracyclines and other drugs such as nonsteroidal anti-inflammatory drugs that decrease renal clearance of lithium.

Many classes of drugs are metabolized by the hepatic cytochrome P450 (CYP) enzyme system, and interactions can occur when a drug metabolized by a particular cytochrome P450 isozyme is coadministered with an inhibitor of the isozyme. There are 4 major families of isozymes involved in the metabolism of antidepressants and the mediation of drug interactions: 3A, 2D, 1A, and 2C.

CYP3A isozymes are the most abundantly expressed in the CYP450 system, and inhibition of isozyme CYP3A4 has the most clinical significance since this isozyme is responsible for metabolizing more drugs than other isozyme systems.[7] Clinically serious drug interactions can occur when an inhibitor of CYP3A4 is given concurrently with terfenadine, astemizole, steroids, or certain benzodiazepines (alprazolam, triazolam). Among the selective serotonin reuptake inhibitors (SSRIs), norfluoxetine, the active metabolite of fluoxetine, is the most potent inhibitor of CYP3A4, followed by sertraline and fluvoxamine. Nefazodone is also a potent inhibitor of CYP3A4.[8] Paroxetine and citalopram have only negligible inhibitory activity at CYP3A4.

The most-studied isozyme is CYP2D6, which is responsible for metabolizing TCAs, neuroleptics, and class I antiarrhythmic agents.[8] Inhibition of CYP2D6 can result in significant increases in blood drug levels with potentially serious consequences. For example, an increase in the blood levels of the TCAs, which have potent class I antiarrhythmic activity, poses a risk of arrhythmias in patients who have had a myocardial infarction.[9] Fluoxetine and paroxetine are potent in vitro inhibitors of CYP2D6,[7] but, in vivo, only norfluoxetine is likely to have clinically significant effects on CYP2D6.[10] Norfluoxetine also has an extended half-life (1 to 2 weeks) that prolongs the window during which drug interactions can occur after withdrawal of fluoxetine treatment. Citalopram, fluvoxamine, and sertraline have mild-to-moderate inhibitory activity at CYP2D6.[8,11]

Isozyme CYP1A2 is less important than isozymes CYP3A4 and CYP2D6, although it metabolizes several drugs frequently administered to elderly patients such as clozapine, olanzapine, tacrine, donepezil, and theophylline; caffeine is also metabolized by this enzyme. Of the SSRIs, only fluvoxamine is a potent inhibitor of CYP1A2.[12]

CYP2C isozymes also play a role in drug metabolism via isozymes CYP2C9 and CYP2C19 in particular. Fluoxetine and fluvoxamine are potent inhibitors of these isozymes.[7,8] Citalopram also has some inhibitory activity.[13] No inhibitory effect has been reported with paroxetine.

Three types of pharmacodynamic drug interactions are extremely important in the patient with late-life depression. These involve drugs with sedative, hypotensive, and anticholinergic properties. For example, excessive drowsiness is a common problem in patients prescribed 2 or more sedative drugs, such as a TCA and a benzodiazepine. Resulting daytime somnolence may cause further wakefulness or agitation at night, for which the patient is commonly administered further hypnotics, thus setting up a vicious cycle. Coadministration of a TCA with other α_1-adrenergic antagonists can result in postural hypotension, increasing susceptibility to falls and fractures. Concurrent administration of a benzodiazepine and a TCA can also increase the risk of falls in the elderly patient. Finally, anticholinergic drug interactions are the most common and serious of the potential interactions in this age group. Medications with anticholinergic properties can cause confusion, disorientation, agitation, and dementia-like syndromes.[14] Despite improved prescribing practices, considerable numbers of patients, particularly those in nursing homes and assisted living facilities, often still receive several anticholinergic drugs simultaneously.

Compliance

Noncompliance is a common problem among the elderly, with evidence to suggest that approximately one third of the elderly do not take antidepressant drugs as prescribed.[15] This is probably an underestimate; older patients may not always admit that they are taking less than the prescribed dose. In the United States, the main reason given by elderly patients for taking less medication than prescribed is drug-related side effects. Common TCA side effects leading to noncompliance are sedation and peripheral anticholinergic effects such as constipation. Although SSRI side effects less commonly lead to noncompliance, agitation on the initiation of treatment may cause inappropriate drug discontinuation. If necessary, blood levels of TCAs can be measured if noncompliance is suspected.

Other factors compromising compliance in the elderly include practical considerations: the inability of the patient to read the label, open the container, or administer the correct dose (for example, if a pill has to be cut in half or a liquid medication has to be poured). These barriers to medication are particularly common in patients who have to take multiple medications, often with different dosing schedules.

Less frequently, elderly patients may take more of their antidepressant medication than prescribed. Common reasons for doing so are forgetfulness, lack of awareness, and the belief that 2 pills will be more effective than 1.

DOSING CONSIDERATIONS

Initial Therapy

In general, it is recommended that antidepressant therapy is started at a low dose in the elderly, followed by a gradual dose increase up to the therapeutic range. Many clinicians use a lower (one-half) starting dose than that recommended for younger adults. Citalopram labeling recommends a starting dose of 20 mg/day in the elderly, for example. However, clinical studies with citalopram show conflicting data regarding the optimal dose of citalopram for treating late-life depression,[16,17] and many clinicians believe that 20 mg is insufficient to provide clinically significant improvement of symptoms. Blood levels of the TCAs correlate with response and toxicity. Studies with desipramine and nortriptyline, and to a lesser extent imipramine, clearly indicate that therapeutic blood levels in older people are approximately equivalent to those for young and middle-aged adults,[5,18] that is, in the 100- to 150-ng/mL range. There are no comparable blood level studies with the SSRIs or venlafaxine, nefazodone, bupropion, mirtazapine, or reboxetine. It is important to note, however, that many clinicians are reluctant to achieve therapeutic doses of the TCAs in elderly patients because of the drugs' potential to cause serious side effects.

There is some controversy concerning the onset of response to antidepressant drugs in elderly patients, probably reflecting the heterogeneity of this population. It is generally believed that the time required for a full therapeutic response is longer than in younger patients and that the treatment period required increases with patient age. This is an area that requires further study.

Maintenance Therapy

Evidence now shows that maintenance therapy prevents the relapse and recurrence of depression in elderly patients in the same manner as in young and middle-aged adults. The SSRIs paroxetine, sertraline, and fluoxetine have been shown to prevent relapse and recurrence in elderly patients for periods of at least 1 year and in some cases up to 2 years.[19] Elderly patients who achieve a good therapeutic response to an antidepressant should be maintained on the same drug and dose of therapy that produced remission of the acute episode for as long as possible.[18,19] It is, therefore, vital that patients are prescribed a well-tolerated drug to ensure that they do not prematurely discontinue treatment.

CONCLUSIONS

In conclusion, the optimal management of late-life depression requires an understanding of the altered pharmacokinetics and pharmacodynamics of antidepressants in the elderly, who in general require lower drug doses than younger patients. Since elderly depressed patients frequently require multiple drug therapy for comorbid disorders, the potential for drug interactions and the issue of compliance also need to be considered. Finally, patients should be prescribed adequate treatment, in both the dose and duration of therapy, to prevent relapse or recurrence.

Drug names: alprazolam (Xanax and others), bupropion (Wellbutrin), citalopram (Celexa), clozapine (Clozaril), desipramine (Norpramin and others), donepezil (Aricept), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil), reboxetine (Vestra), sertraline (Zoloft), tacrine (Cognex), triazolam (Halcion), venlafaxine (Effexor).

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Discussion

Management Considerations for Late-Life Depression

Dr. Montgomery: What are the key recommendations from your presentation?

Dr. Salzman: One of the simplest and most critical recommendations for our medical colleagues is to take a comprehensive history of drugs the older person is taking, including over-the-counter drugs and herbal preparations. Polypharmacy is very important data.

The second recommendation, which is generally accepted in the United States, is to use selective serotonin reuptake inhibitors (SSRIs) as the first-choice antidepressant drug for an older person who has not previously been treated with SSRIs. The SSRIs now offer efficacy and safety and have replaced tricyclics as the first-choice drug class, and this includes seriously, severely depressed older patients, even those in the hospital.

We do not have data for the equivalent efficacy of miscellaneous or atypical drugs. Some data suggest that venlafaxine is effective, but we have no data for nefazodone, bupropion, or mirtazapine.

Dr. Zisook: Would you say SSRIs are first choice, and we need more studies on the other newer drugs?

Dr. Salzman: They are certainly the first choice versus tricyclics, which were the standard. I would no longer consider a tricyclic antidepressant the first choice in the older patient and only use them if that patient had previously responded to tricyclics and had not responded to an SSRI.

Dr. Montgomery: You indicated that depression in the elderly should be treated aggressively.

Dr. Salzman: I am going to add that the geriatric slogan, "start low and go slow," needs a third component, which is "don't quit too soon." My own clinical sense is that older people are undermedicated because either the clinician, the patient, or the family think the depression is appropriate to their stage of life.

Some doctors are unacceptably timid about using these medications for a suffering elderly person. It does mean balancing therapeutic effect and side effects. As a group, older people may be more sensitive to side effects, or the pharmacokinetics of drugs are altered and there is the potential for interactions, but we should use the drugs and be reasonably aggressive.

Dr. Zisook: Unfortunately, polypharmacy is the standard of care even among psychiatrists in the United States. They often start with an SSRI, but immediately add benzodiazepines or trazodone, for example, to counter sleep or anxiety. Should we say that monotherapy is the treatment of choice, at least initially?

Dr. Salzman: I agree with your proposition, but I actually use a certain amount of polypharmacy myself. I think trazodone is a useful drug in the elderly, as are benzodiazepines when they are used judiciously and carefully, for a relatively brief period of time. But I don't think that we can make any statement about standard of care, because this is such a heterogeneous group. From a kinetic and dynamic point of view, body changes in this age group are variable, so we have to consider heterogeneity and not just describe guidelines for all older people.

Dr. Sadavoy: We have come to the conclusion that a variety of stressors get translated into depressive disorder in some form or another, but the approach to the management of stress is multifaceted and is only in part a pharmacologic approach. Also, we have to cope with data sets around the importance of issues of intimacy, for example, social support and relationships and their impact on depression and depressive disorder. The data are conflicting, but cannot be ignored in the context of the elderly; the way the therapist approaches the patient and the importance of the therapist's role in management are crucial.

Dr. Salzman: My article focused on pharmacologic management because there are limited data on nonpharmacologic treatment, largely related to minor depression in the elderly, that resulted from some well-conducted studies using good techniques. But there is little information about psychotherapy in the severely depressed elderly person, and I think psychotherapy for severe depression is of limited benefit for the elderly as for the nonelderly. It is probably most useful in helping to maintain compliance rather than having a direct therapeutic impact. It's only after the severely depressed person starts to respond that psychotherapeutic interventions, in the broader sense of the term, may be useful. A treatment program should include nonpharmacologic components, and medication should be prescribed in the context of thoughtful interpersonal management.

Dr. Zisook: One specific recommendation is that any comprehensive treatment approach requires education of the patient and his or her family, a relationship between the physician and the patient and family, and psychotherapy where indicated. The more persistent, pervasive, and severe the depression, the more important early psychopharmacologic intervention becomes.

Dr. Beekman: We should specify that treatment should be structured in acute and continuation phases as in younger adults.

Dr. Zisook: We are advocating longer-term treatments rather than simply the remission of symptoms.

Dr. Salzman: We have been talking about data for the elderly aged less than 75 or 70 years. There are few data for older patients. Our nursing home study (manuscript submitted) looked at patients aged over 80 years who were nondemented and had subsyndromal depression. Those patients with a large number of symptoms, mostly depressive symptoms but some anxiety, did better on paroxetine treatment than placebo.

Our study showed a high placebo response rate, indicating that just working with these individuals was a very effective antidepressant for them because they had support. When we looked at subsamples, we began to see a meaningful difference between the paroxetine- and placebo-treated individuals.