Depression and Dementia: What Clinicians Need to Know (Part 3)

The selection of an antidepressant agent for elderly patients requires the consideration of several factors, including safety, tolerability and efficacy. The presence of dementia adds importance to such issues as compliance enhancement and overdose safety. The final installment of this series of articles provides an overview of the phamacologic treatment of depression in this patient population.

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In the two previous articles, we discussed the evaluation process, including the easy way to remember the criteria for a major affective disorder, using the acronym "SIG: E CAPS," in the elderly. Non-pharmacologic approaches and the special issue of suicidal risk also were discussed.[1,2] Before exploring pharmacologic issues, we must again underline that, if close to 60% of AD patients will suffer a depression during the course of their illness, the number of caregivers describing themselves as depressed is actually higher than 60%. It is, therefore, easy for the family physician to understand that this can affect not only the quality of life of the caregiver, but also the quality of the care they can give the AD patients.

Pharmacologic Therapy

Pharmacologic treatment in the elderly is complicated by a number of factors.[3] These include:

- ***Physiologic changes***. Decreased distribution, prolonged half-life, and effects of hepatic and renal function on metabolism all can affect pharmacokinetics, requiring dosage adjustement and/or titration.
- ***Sensitivity to adverse effects.***
- ***Drug-drug interactions from polypharmacy.*** Elderly patients often take several prescribed and non-prescribed medications daily.
- ***Increased risk of falls and, therefore, fractures*** with medications that cause sedation or orthostatic hypotension.

Considerations in choosing an antidepressant, in the elderly, include: long-term safety, tolerability and efficacy; rapid onset of action; limited drug-drug interactions; less chance of fatality with accidental or deliberate overdose; lack of sedation; and no cardiovascular toxicity. Though not a necessity, once-daily dosing can be useful to enhance compliance.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) generally are no longer considered first-line therapy for depressed elderly patients. They are, nonetheless, effective in the treatment of many depressive disorders. The potentially serious anticholinergic, adrenergic and histaminic effects of tertiary TCAs, such as amitriptyline, imipramine or clomipramine, can lead to early discontinuation of treatment and failure to achieve therapeutic dose levels. These effects include:

- Slow cardiac conduction with serious risk of arrhythmias and heart block.
- Risk of orthostatic hypotension leading to falls and fractures.
- Possibility of tachycardia in patients with cardiac insufficiency.
- Impairment of cognitive function.
- Delirium and even seizure with high plasma levels.
- Dry mouth, constipation, urinary retention.
- Daytime sedation.

Secondary TCAs, however, have far fewer of these side effects. If a patient has been successfully treated for a depression with amitriptyline in the past, nortriptyline can be very useful, particularly if sedation is required. If a patient has responded to imipramine in the past, desipramine would be the drug of choice, particularly if sedation is not desired.

Selective Serotonin-Reuptake Inhibitors

Selective serotonin-reuptake inhibitors (SSRIs) are generally considered first-line treatment for elderly depressed patients for a number of reasons,[4] including:

- Efficacy has been well-documented in elderly patients.
- Beneficial pharmacologic profile. SSRIs and/or metabolites with a shorter half-life (citalopram, paroxetine, sertraline) reduce the risk of accumulation, and of drug-drug interactions after discontinuation.
- Generally well-tolerated. Adverse effects include nausea, diarrhea, insomnia, headache, agitation and sexual dysfunction. They also are well-tolerated in patients with physical illnesses, including poststroke patients and those with cardiac disease.
- Minimal changes in cardiac conduction (ECG).
- No significant orthostatic hypotension that could cause dizziness or falls.
- Minimal associated sedation or reduced alertness, though individual SSRIs vary in effect. Minimal anticholinergic effects with reduced risk of delirium, memory impairment, urinary retention, etc.

For all drugs metabolized by the hepatic P-450 enzyme system, delayed clearance and prolonged accumulation can result if the P-450 enzymes are deficient or inhibited. Different P-450 isoenzymes are involved with the metabolism of different SSRIs. SSRIs also may inhibit P-450 isoenzymes that are responsible for their metabolism and those that are not appreciably involved in their metabolism. For example, the isoenzyme CYP2D6, the best understood isoenzyme, is integral to the metabolism of a wide variety of drugs. It is mildly inhibited by citalopram, fluvoxamine and sertraline, but more inhibited by paroxetine and fluoxetine.

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Psychotropic medications, including SSRIs, have the potential to induce hyponatremia. Hyponatremia typically develops in the first two weeks of treatment or dosage escalation. It can generally be treated successfully with discontinuation of medication and fluid restriction.

Serotonin syndrome can occur when more than one serotonergic drug, each selective for a different serotonin receptor, are taken together. The syndrome is characterized by reversible confusion, agitation, fever, rigidity and neuromuscular complications, but, in its most extreme form, can result in coma or even death. When prescribing an SSRI, care should be taken to ensure that the patient is not taking other serotonergic agents, including prescription, non-prescription or herbal products. Monoamine oxidase inhibitors (MAOIs) are included in this group of drugs that should not be taken with SSRIs, and these agents should be washed out fully before switching from one class to another.

Monoamine Oxidase Inhibitors

Because of their potential for serious adverse effects, including orthostatic hypotension at relatively low doses and general lowering of blood pressure, as well as life-threatening effects with tyramine-rich food products and sympathomimetic drugs (including medication in non-prescription cough-cold products), irreversible MAOIs are not considered first- or second-line treatment in the elderly. They may be effective for some subpopulations, including patients unresponsive to other antidepressants.

Reversible MAOIs, such as moclobemide, have been shown to be well tolerated for treatment of depression in the elderly. This medication is well-tolerated, and the most common side effects are nausea, insomnia and restlessness. Patients do not require dietary restriction while taking moclobemide, but those with hepatic impairment require reduced doses. Serotonin syndrome can be prevented by avoiding simultaneous medication with other serotonin-receptor inhibitors, including SSRIs.

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Other Agents

Nefazodone has been shown to have no unusual age-related phemonema. However, side effects such as sedation, dizziness and constipation can occur, and are problematic in elderly patients.

Trazodone is used, much more frequently, as a mild sedative or a sleeping medication. Small doses (25-100 mg) are used. In larger doses, trazodone can be used to treat depressed geriatric patients, as it is associated with very few anticholinergic side effects and is safe in cases of overdose. However, in those larger dose, it can be responsible for sedation, impaired cognition, and orthostatic hypotension.

Venlafaxine is a reasonable choice or alternative in the elderly population. It has minimal anticholinergic side effects but can cause insomnia and restlessness.

Dosing Guidelines[3,5]

General medical practice with elderly patients is to start pharmacotherapy at low doses and titrate slowly. This is true for antidepressants, but it is important to remember that therapeutic doses frequently are the same as for a much younger population. For this reason, a tendency to underdose antidepressants in the elderly can lead to unsuccessful treatment. For example, therapy can be initiated with sertraline 25 mg or citalopram 10 mg for the first week or two, but should be doubled to the usually therapeutic dose after that time. After six weeks, if the patient is not responding to the medication but is tolerating it well, a dose increase can be useful. Therapy should be maintained at the effective dose and not be reduced for long-term maintenance.

Course of Treatment

The first phase of therapy is intended to bring the current episode of depression into remission. Regardless of which agent is chosen for the initial course of therapy, it is critical to have an adequate therapeutic period of at least six weeks before evaluating the efficacy of treatment. As mentioned above, if there is little or no improvement, the dose of the agent should be increased, if tolerated, and reassessed after four to six weeks. If there still is no response, the physician can again increase the dose or switch to another agent (either from the same class or another class), and repeat the process of evaluating efficacy. Wash-out periods differ for various agents, but it is clear that this process can be lengthy, and this information must be shared with the patient and/or caregiver to encourage patients and ensure compliance.

Upon achieving an adequate response, the following courses of therapy should be taken:

- ***Continuation treatment,*** initiated after acute therapy, to prevent a relapse of the initial episode (for about six to eight months).
- ***Maintenance therapy*** should be considered for patients with a history of one or more episodes of major depression (particularly in the last five years), or for any patient at risk of recurrence (*i.e.,* first episode after the age of 65 years).
  - Two-year full-dose maintenance for all elderly patients.
  - Potentially lifetime full-dose maintenance for elderly patients with three or more episodes.

Regular follow-up visits (every three months, for example) should be scheduled to monitor efficacy, side effects and compliance, and to avoid undetected relapse or recurrence.

At any point in therapy, the physician may choose to consult with or refer the patient to a psychiatrist, who may re-evaluate the current regimen, initiate or recommend combination pharmacotherapy, or even recommend electro-convulsive therapy (ECT), which has been proven safe and effective in elderly patients with depression.

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Discontinuing Medication

If or when discontinuation of medication becomes necessary, drug therapy should be tapered over a period of several weeks, rather than stopped abruptly. SSRIs should be tapered over one to two weeks to minimize discontinuation syndrome (which is characterized by dizziness, fatigue, nausea, pain and agitation), and wash-out should be completed before initiating another agent.

References:
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