Pharmacological Treatment of Depression

by ROBERT C. YOUNG, MD

This article highlights treatment issues for elderly depressed patients. Nevertheless, depressive disorders occur throughout the life span, and there are fundamental similarities in the general approach to the pharmacologic management of major depression in the elderly and in younger adults.

The first similarity is that the same classes of drugs can be used effectively in both age groups. Second, management in both age groups focuses both on acute symptom reduction and on the longer term objectives of maintaining symptom reduction and preventing recurrence or relapse. Third, clinical decision-making similarly involves weighing risks and benefits of particular drug regimens.

The general pharmacologic distinction between pharmacokinetics and pharmacodynamics is an issue highlighted in the treatment of the elderly. Pharmacokinetics refers to the processes of drug absorption, metabolism, distribution, and excretion, and their resulting drug concentrations in body compartments at particular times. Pharmacodynamics refers to the effects of a drug on tissue function, including reduction of signs and symptoms of illness and toxicity.

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**WHY TREAT?**

Major depression is clinically important in the elderly, as in other age groups, because it can respond to acute treatment and prophylaxis. Recent follow-up studies have emphasized the need for adequate treatment in elderly depressives. Effective intervention can reduce morbidity and perhaps mortality.

**WHAT TO TREAT**

Major depressive episodes are a prevalent form of affective disorder in the elderly; with this syndrome, diagnostic reliability can be high. Less is known about dysthymia, a
milder syndrome for which diagnostic reliability may be lower.

There has been only limited examination of clinical predictors of response to treatment in late-life major depression.\(^3\) Issues that especially require further investigation in the elderly include index age, age at illness onset, concomitant medical illness, and concomitant cognitive impairment or dementia.

Some predictors might be extrapolated from studies in younger adults\(^4\) but need verification in the elderly. These predictors include psychosis (i.e., delusions and hallucinations), a negative predictor of response to antidepressant alone. Both prolonged duration of episode and prior treatment with an adequate trial of an antidepressant during the index episode are negative predictors of response to additional pharmacotherapy.

Other clinical distinctions have also received limited investigation as predictors. Some are based on illness state, such as overall severity and relative preponderance of endogenous or melancholic features. Others include polarity, i.e., unipolar versus bipolar illness, and chronology, i.e., primary versus secondary illness.

Laboratory correlates of major depression in the elderly are described elsewhere in this issue (see “Biological Markers in Geriatric Depression” by L.S. Schneider, MD, pp 83-91); these include measures of brain morphology\(^5\) and indirect measures of brain function. Preliminary suggestions of relationships to treatment response require further investigation.

**Table: Pharmacokinetic Issues and Cyclic Antidepressants in the Elderly**

<table>
<thead>
<tr>
<th>Age</th>
<th>Drug Interactions</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Decreased gastric pH and motility; decreased intestinal surface area and blood flow: none known</td>
<td>Antacids, anticholinergics: delayed/decreased absorption</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Decreased hepatic blood flow; decreased enzyme activity: may decrease demethylation</td>
<td>Barbitalates increase metabolism; neuroleptics/methylphenidate/cimetidine decrease metabolism; decreased and increased plasma concentrations, respectively</td>
</tr>
<tr>
<td>Distribution</td>
<td>Increased body fat/lean ratio: decreased and increased plasma concentrations of parent compounds</td>
<td>Phenytoin/phenybutazone: increased plasma free fraction</td>
</tr>
<tr>
<td>Excretion</td>
<td>Decreased renal clearance of hydroxylated metabolites: increased plasma concentration</td>
<td>Renal disease: increased plasma unconjugated</td>
</tr>
</tbody>
</table>

**Continuation and Maintenance/Prophylaxis**

Following satisfactory acute response to antidepressant pharmacotherapy, continuation treatment is indicated for at least several months. Similarly, following a successful ECT course, thymoleptic pharmacotherapy is generally instituted in an effort to reduce the risk of relapse in the first few months. Frequently recurring illness is an indication for maintenance somatic treatment.

**Where to Treat**

In an acute treatment situation, the decision needs to be made whether outpatient management or hospital inpatient care is optimal. In
the elderly, nursing home facilities can represent an approximation to hospital care.

One type of indication for hospital-based acute care is clinical severity, e.g., suicidal ideation and acts, physical debilitation, delusional or hallucinatory phenomena, and agitation. Another type of indication is clinical complexity, e.g., associated medical problems that make close monitoring essential and the presence of one or more concurrent psychiatric disorders, such as substance dependence or dementia.

**HOW TO TREAT**

**Baseline Assessment**

Somatic treatment assumes an adequate review of physical health and other drug treatments. This should include a recent physical examination and electrocardiogram. Such review identifies any factors that may contribute to depression—so-called organic affective syndromes. Such factors should be corrected if possible prior to specific antidepressant treatment, since this in itself may lead to amelioration of symptoms.

Such review also identifies medical conditions or drugs that might complicate antidepressant pharmacotherapy. Medical conditions and other drugs can interact with antidepressant pharmacotherapy either at the pharmacokinetic or pharmacodynamic level. Examples of such interactions with polycyclic antidepressants at the pharmacokinetic level are listed in the Table. Treatment with L-dopa and other sympathomimetics are contraindications to the use of monoamine oxidase inhibitors (MAOIs).

Drugs that potentially interact with polycyclic antidepressants at the pharmacodynamic level include sedatives, antiarrhythmics, and diuretics. Physical conditions that potentially interact with polycyclic antidepressants at the pharmacodynamic level include untreated glaucoma and prostatic hypertrophy; pretreatment orthostatic hypotension is a predictor of increased orthostatic change during treatment, and pretreatment intracardiac conduction delay predicts greater degree of conduction abnormality during treatment.

**Other Somatic Treatment**

Electroconvulsive therapy (ECT) needs to be considered as an alternative to drug treatment (see “Electroconvulsive Therapy in the Elderly” by L. Greenberg, MD, and M. Fink, MD, pp 99-101). Considerations in favor of ECT include medical conditions that can potentially complicate drug treatment, active suicidality, impairment in food and fluid intake that is life threatening, presence of psychosis, and prior lack of response to pharmacotherapy.

**Drug Selection**

The choice of a particular antidepressant agent is based first on minimizing potential interactions with any medical conditions and concurrent drug treatments. Further, the history of previous antidepressant pharmacotherapy and associated response, both in prior episodes and in the current episode, must be carefully considered.

In elderly major depressives without delusions, tricyclic antidepressants (TCAs) have been a mainstay of treatment. The secondary amine TCAs, such as nortriptyline and desipramine, have a lower side effect profile, including sedation and anticholinergic effects, compared to tertiary amine TCAs; this may be related to differences in their affinities for certain neurotransmitter receptors. Further, nortriptyline has a low potential for inducing orthostatic hypotension. However, protriptyline, another secondary amine TCA, has the disadvantage of a long half-life.

The MAOIs also are effective in acute treatment of geriatric major depression. Phenelzine and tranylcypromine are most often used. Treatment with MAOIs requires dietary restriction.

Newer agents, such as trazodone, fluoxetine, and bupropion, can be effective in the elderly. They share a limited history of use in the elderly compared to TCAs, and it is unclear whether their more narrow spectrum of pharmacologic activity reduces their overall efficacy. However, they do appear to have lower potential for certain side effects than tertiary amine TCAs.

**Adequacy of Treatment Trial**

In geriatric patients, clinicians generally begin with the single daily (usually at bedtime) administration of a low dose, which is increased gradually. When a patient does well early in treatment, clinicians continue whatever dose has been reached. Adequacy of antidepressant drug treatment only becomes a clinical issue when response is poor; it is defined by quantity and by duration.

Daily dosage represents one measure of drug exposure. Plasma (or serum) concentrations of TCAs represent a better index of tissue exposure to drug than does daily dose. This is because individuals of all ages vary widely in hepatic metabolism of antidepressants.

Age-related changes in physiology can alter the pharmacokinetics of antidepressants and other thymoleptic drugs; these changes are outlined in the Table. Plasma concentrations of secondary amine TCAs are similar in elderly patients compared to younger patients treated with similar doses. Increases in unconjugated hydroxylated metabolite concentrations may be noted in some elderly patients compared to younger patients treated with similar...
doses of secondary amine TCAs. Some evidence indicates increased tertiary amine TCA concentrations in elderly patients compared to young patients.

Plasma concentrations of antidepressant following test doses predict steady state concentrations. Dose increments at steady state generally produce proportional changes in plasma concentrations.

Duration of exposure to a particular concentration or dose of drug represents the other critical factor in pharmacotherapy. The time course of therapeutic response in major depression is variable between individuals, ranging from days to weeks. While this is true in all age groups, it has been proposed that the time course of response may be prolonged with increased age. At least 6 weeks is required to judge full therapeutic impact. Clinical experience suggests that failure to demonstrate any response within several weeks may be an indicator of poor overall response.

**Monitoring Antidepressant Treatment**

Therapeutic response in the elderly is judged from mental status examination and from observation by family or other care givers. In patients with significant cognitive impairment, assessments of depressive psychopathology may need to derive substantially from observed behavior. Brief rating scales for evaluating severity of depressive state may be helpful to clinicians.

The anticholinergic side effects of TCAs include increased heart rate, increased urinary sphincter tone, constipation, and impaired pupillary accommodation. Central anticholinergic toxicity in the form of delirium also can occur. MAOIs have relatively low anticholinergic effects.

The cardiovascular side effects of TCAs include, in addition to increased heart rate, orthostatic hypotension and quinidine-like prolongation of intracardiac conduction. Periodic monitoring of the electrocardiogram and of orthostatic blood pressure changes are necessary during treatment. The MAOIs produce orthostatic hypotension but are associated with little tachycardic effect or conduction change.

The new antidepressant compounds—trazadone, fluoxetine, and bupropion—have a relatively low propensity for anticholinergic effects. They also have few cardiovascular side effects, although trazadone does produce orthostatic hypotension.

In poor responders, plasma or serum concentrations of antidepressant can be helpful in detecting noncompliance and in individualizing dosage in order to optimize benefit.

Orderly relationships between plasma concentration and therapeutic effects have been observed for some TCAs, such as nortriptyline, in young adults with major depression. Although these relationships have not been similarly tested in elderly patients, these patients can respond to secondary amine TCAs at plasma concentrations effective in younger patients. Clinical lore suggesting that older patients systematically require a lower quantity of antidepressant exposure has not been verified. Whether active metabolites modify therapeutic response in the elderly, as has been suggested in younger adults, remains to be established.

Some toxic effects of TCAs are linearly related to plasma concentrations, and delirium has been associated with high plasma concentrations. Increases in heart rate can be weakly positively correlated with plasma TCA concentrations. Quini-
increased vulnerability to tardive dyskinesia.

Bipolar disorder is less common than major depression in the elderly, as with younger patients. However, the pharmacotherapy of bipolar patients with depressive syndromes involves special considerations. Clinicians may first increase the dose and plasma level of lithium or other mood stabilizer, such as carbamazepine, to alleviate depressive symptoms. Lithium levels ranging from 1.0 mEq/L to 1.4 mEq/L are optimal in this situation, if tolerated. Failing that, patients should continue to receive such drugs in conjunction with an antidepressant agent to reduce the potential risk of manic state.

**Unsatisfactory Response to Adequate Treatment**

When response to an adequate drug trial is poor, several issues arise. First is the need to characterize the response. Patients who respond poorly to antidepressants may be distinguished from those with a negligible response; in the former case, consideration may be given to potentiation of therapeutic response by addition of a new agent; in the latter case, a different antidepressant probably needs to be considered. Second, poor response is an opportunity for further review of diagnosis. For example, in the elderly if cognition worsens during treatment, this raises the question of an underlying organic mental syndrome, and the completeness of medical history and workup should be reviewed. Again, the presence of delusional features has specific treatment implications and may not be immediately apparent.

Potentiation of partial antidepressant response by thyroid hormone, lithium salts, or addition of another antidepressant drug can be effective in some patients in the general population and should be considered in elderly patients as well. Careful consideration and monitoring of cardiovascular status is needed if thyroid hormone is used. If lithium is added, the initial dosage must be low (eg, 150 mg/day). The dosage then is increased gradually, and levels are monitored carefully because of the decreased renal clearance of lithium in the elderly; diuretic use does not preclude lithium use but necessitates even more conservative dosage as lithium excretion is diminished by diuretics.

When considering a second somatic treatment, the first decision is whether to use an alternative drug or electroconvulsive therapy. In a mild to moderately symptomatic inpatient or outpatient in whom time constraints are not primary, another antidepressant may be tried. However, the rate of response to a second antidepressant drug, given the lack of response to an initial adequate treatment trial, presumably will be low in the elderly as it is in younger adults.

Clinicians lack clinical or laboratory predictors of differential response to specific antidepressant agents. Therefore, in selecting a second antidepressant drug, clinicians are still guided primarily by toxicity profiles.

**Continuation and Maintenance/Prophylaxis**

Beyond the management of acute depressive episodes, pharmacotherapy can make an important contribution to reducing relapse. These issues are especially important in elderly patients, who may be at higher risk of relapse than younger patients.

The situation in which there has been good response to an antidepressant is the most straightforward. Continuation of that drug for a period of 6 to 18 months before gradually tapering off the dosage seems warranted. Anecdotical literature in younger patients has suggested that dosages, and plasma levels, used acutely should be maintained, rather than being immediately reduced arbitrarily.

The efficacy of a drug in acute treatment may not be strictly related to its prophylactic efficacy in a particular patient. Nevertheless, when a patient has responded to ECT and has no clear history of response to a particular antidepressant or class of antidepressant, clinicians generally select a new class of thymoleptics empirically as long as it can be well tolerated.

All of the antidepressants can be used for maintenance. Recent investigation in elderly outpatients has supported the efficacy of phenelzine and nortriptyline for this purpose and has suggested that phenelzine may in fact be superior. Further, lithium salts are often overlooked as an option in recurrent major depression, despite their being relatively well tolerated.

The importance of compliance with outpatient treatment must be emphasized. When cognitive or physical limitations are present, these may add to the risk of noncompliance in elderly patients. If patients are treated with MAOIs, compliance with dietary and drug restrictions are as critical as medication compliance.

**Other Treatment Modalities**

Both in acute and long-term management, the use of thymoleptics should be considered carefully with other therapeutic strategies. In the acute treatment setting, this includes supportive psychotherapy (see “Psychotherapy of Depression in the Elderly” by P.J. Moberg, MD, and L.W. Lazarus, MD, pp 92-96), including recommendations of deferral of major decision-making and education of patients and their families or other care givers about the nature of depressive illness. Working closely with other physicians managing medical issues is critical in...
elderly patients. Further, considera-
tion must be given to community
resources that can be used to coun-
teract social isolation and inactivity
if these are long-term problems.
However, final evaluation of the pa-
tient's long-term needs often must
be deferred until acute symptoms
have been alleviated because behav-
ioral competence can be strikingly,
but potentially reversibly, impaired
by depressive states.

REFERENCES
1. Baldwin RC, Jolley DJ. The prognosis
1986; 149:574-583.
2. Klerman GL. Depressive disorders: Fur-
ther evidence for increased medical mor-
bidity and impairment of social function-
ing. Arch Gen Psychiatry. 1989; 46:856-
858.
3. Blazer DG II. Depression in Late Life. St.
4. Joyce PR, Paykel ES. Predictors of drug
response in depression. Arch Gen Psychiatry.
5. Young RC, Nambudiri D, Alexopoulos
GS, Roe R, Deck M. Ventricular-brain ratio
(VBR) and response to nortriptyline in
geriatric depression. Abstracts. Annual
Meeting of the Society of Biological Psy-
chiatry; 1988.
6. Salzman C. Clinical Geriatric Psy-
Hill; 1984.
7. Glassman AH, Bigger JT Jr, Giardina EV,
et al. Clinical characteristics of imipram-
ine-induced orthostatic hypotension.
8. Roose SP, Glassman AH, Giardina EGV,
et al. Tricyclic antidepressants in de-
pressed patients with cardiac conduction
disease. Arch Gen Psychiatry. 1987;
44:273-275.
9. Potter WZ, Linnoila M. Tricyclic an-
tidepressant concentrations: clinical and
research implications. In: Post RM, Bal-
lenger JC, eds. Neurobiology of Mood
Disorders. Baltimore, Md: Williams and
Wilkins; 1984:698-709.
10. Georgotis A, McCue RE, Hapworth W,
et al. Comparative efficacy and safety of
MAOAs versus TCAs in treating depres-
sion in the elderly. Biol Psychiatry. 1986;
21:1155-1166.
11. Young RC, Alexopoulos GS, Shamoian
CA, Manley MW, Dhar AK, Kutt H.
Plasma 10-hydroxy-nortriptyline in eld-
12. Nelson JC, Jatlow P, Mazure C. De-
sipramine plasma levels and response in
elderly melancholic patients. J Clin Psy-
13. Alexopoulos GS, Abrams RC, Young
RC, Shamoian CA. Cornell scale for de-
pression in dementia. Biol Psychiatry.
14. Young RC, Alexopoulos GS, Shindle-
decker R, Dhar AK, Kutt H. Plasma
10-hydroxy-nortriptyline and therapeutic
response in geriatric depression. Neurops-
15. Preskorn S, MacDS. The implication
of concentration/response studies of tricy-
clic antidepressants for psychiatric re-
sponse and practice. Psychiatr Dev.
1984; 2:201-222.
Electrocardiogram changes and thera-
pic desipramine and 2-hydroxyde-
sipramine concentrations in elderly de-
17. Schneider LS, Cooper TB, Severson JA,
Zemlenyi T, Sloane RB. Electrocardi-
ographic changes with nortriptyline and
10-hydroxy-nortriptyline in elderly de-
pressed outpatients. J Clin Psychophar-
macol. 1988; 8:402-408.
18. Meyers BS, Greenberg R. Late-life delu-
sional depression. J Affective Disord.
1986; 11:133-137.
19. Exttein I. Treatment of Tricyclic-Resistant
Depression. Wolters, DC2: American
20. Georgotis A, McCue RE, Cooper TB. A
placebo-controlled comparison of nor-
triptiline and phenelzine in maintenance
therapy of elderly depressed patients.
Arch Gen Psychiatry. 1989; 46:783-786.