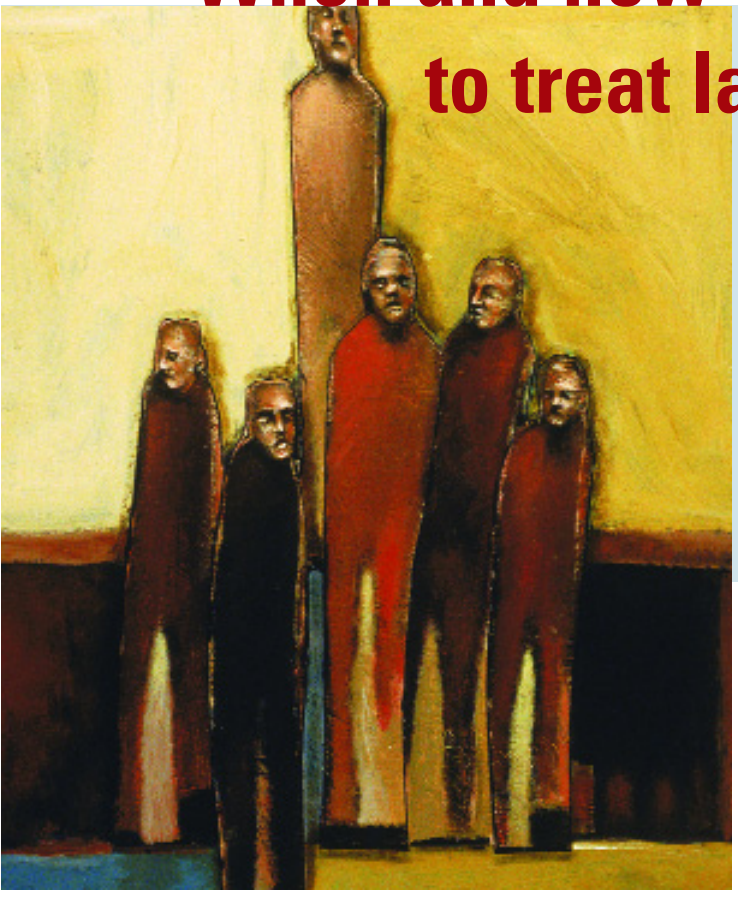
Current PSYCHIATRY

When and how to use SSRIs to treat late-life depression



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When antidepressants are indicated for older patients, our goal is to achieve the maximum therapeutic effect with the lowest effective dosage and minimal side effects

Despite its impact on individuals and public health, depression in older persons is inadequately diagnosed and treated. Even when depression is diagnosed, only one-third of persons older than 65 receive treatment.[1] Reasons for this include:

- lack of physician awareness that depression presents differently in older than in younger adults
- patient denial of depressive symptoms
- patients' and physicians' mistaken belief that feeling depressed is a normal part of aging.

The good news is that when geriatric depression is recognized, it usually responds favorably to treatment, although aggressive intervention may be required.[2] In this article, we describe our approach to diagnosis and discuss use of selective serotonin reuptake inhibitors (SSRIs) as first-line antidepressants for older patients.

Late-life depression risk factors

Depression is common in older persons, especially in those who have experienced psychosocial or medical losses, includ-

Box

CASE REPORT: DEPRESSED, AT RISK FOR SUICIDE

A 72-year-old man presents with trouble concentrating, decreased appetite, anergy, and anhedonia. He says he frequently awakes at 3 AM, and it takes him 2 hours to return to sleep. Lately, he has thought of shooting himself with his hunting rifle. The patient's wife died of cancer 1 year ago, and he has developed several medical illnesses within the past 10 years: chronic obstructive pulmonary disease, worsening arthritis, mild ischemic heart disease, and worsening hearing loss.

The patient denies feeling depressed and instead attributes his symptoms to his medical illnesses. He has become progressively isolated in the past year, with less social contact with his friends at the local parish. His older brother, with whom he was close, died recently. Until now, he says his "pride" has made him resist his primary care physician's recommendation that he see a psychiatrist.

ing chronic illness. Although its presentation often does not meet criteria for major depression, the more common subsyndromal depression is debilitating and can lead to suicide.

Late-life depressive syndromes commonly present with somatic complaints. Typically, patients deny having a mental illness and perceive that their symptoms are organic in origin (*Box*).[1]

Losses. Psychosocial and medical losses are major risk factors for late-life adjustment disorders, subsyndromal depressive disorders, and major depression. Medical losses may include loss of mobility or independent function, chronic pain, or sensory losses that limit one's ability to read or hear. Psychosocial losses may include the death of a spouse, sibling, or peer or moving from one's longtime home to a more structured environment (assisted living, nursing home, or living with relatives).

Medical causes to rule out before starting antidepressant therapy include:

- hypothyroidism
- medication side effects
- bipolar disorder, which may require the use of a mood-stabilizing agent to prevent manic symptoms.[3]

History. Often a history of mood disorder in the individual or a family member can help the clinician determine that mental illness accounts for the patient's symptoms. In older patients, it is not uncommon for psychotic symptoms to accompany a primary mood disturbance.

Suicide risk is high in depressed older persons, so detection and quick treatment of depression is paramount. Older white men are at particularly high risk for completed suicide using firearms.[3]

Alcohol abuse may contribute to depressive symptoms in older persons. A second peak of alcoholism occurs in the eighth decade of life and can confound diagnosis of depression in patients of this age.

Making the diagnosis. In patients who present with symptoms and risk factors for late-life depression, depression rating scales can help confirm the diagnosis. Commonly used scales include the Beck Depression Inventory, the Hamilton Depression Rating Scale, and the Zung Self-Rating Depression Scale. Specialized scales for use in older patients include the Geriatric Depression Scale and the Cornell Scale; the latter scale is designed for patients with comorbid depression and dementia.[3,4]

Treatment

Antidepressant treatment in combination with psychotherapy usually is warranted when treating nonpsychotic late-life depression. In patients with psychosis, electroconvulsive therapy can help achieve remission.

Cognitive-behavioral therapy and interpersonal and insight-oriented psychotherapy have been shown to be effective in late-life depression. Social interventions aimed at preventing isolation also can work. In milder cases of depression, psychotherapy alone may be sufficient.[3]

Starting dosages. When antidepressant therapy is indicated in an older patient, start low and go slow.[5] Older patients generally require prolonged titration rates and a longer course of treatment than do younger patients. Physiologic changes that occur with aging include:

- altered drug metabolism rate, including slower demethylation

- increased body fat-to-water ratio, which increases the volume of distribution for lipophilic psychotropic drugs
- decreased glomerular filtration rate, which may account for higher serum concentrations of drugs and their metabolites
- increased sensitivity of the older brain to the effects of medications.[6]

Thus—with some exceptions—recommended starting dosages for older patients are usually one-half those used in younger adults. For the frail older patient, the starting dosage should probably be even lower—about one-fourth the typical starting dosage in young adults.[6] As in younger patients, the treatment goal is to achieve the maximal therapeutic effect with the lowest effective dosage while avoiding side effects.

More time may be required to achieve a therapeutic effect in older than in younger patients. Substantial improvement may not be seen until an older patient has been taking an antidepressant for 9 weeks or longer. In younger patients, responses are seen as early as 2 weeks after starting antidepressant therapy, and remission occurs within 6 to 8 weeks.[2]

Table 1

USING SSRIs TO TREAT LATE-LIFE DEPRESSION

Drug	Half-life (hours)*	Recommended dosage after age 65 (mg/d) †
Citalopram	35	20 to 40
Escitalopram	27 - 32	10 to 20
Fluoxetine	96 - 386	10 to 60
Fluvoxamine	16	25 to 300
Paroxetine	21	10 to 40
Sertraline	26	25 to 200

* In the older patient, medication half-lives may be extended 1.5- to 2-fold.

† The heterogeneity of aging can lead to a wide variation in antidepressant target dosages. Therefore, although starting dosages for older adults are lower, final dosages may be the same as for younger adults.

Source: *Physicians' Desk Reference (56th ed)*. Montvale, NJ: Medical Economics Co, 2002.

SSRIs versus tricyclics

SSRIs—citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline (*Table 1*)[7]—are considered first-line antidepressants for late-life depression. Although SSRIs and tricyclic antidepressants (TCAs) demonstrate equivalent efficacy in older adults, SSRIs are associated with less-troublesome side effects.[2]

SSRIs are less sedating than tricyclics and are not associated with adverse effects on cognition; both qualities make these agents appropriate for older patients. Risk of overdose with SSRIs also is much lower than with TCAs.[2]

Both types of agent have been reported to cause movement disorders such as extrapyramidal symptoms and even tardive dyskinesia, but these side effects are much more rare with SSRIs than with TCAs.[2] Also—unlike the TCAs—SSRIs do not significantly effect cardiac conduction, which is an important quality in the older population with its relatively high incidence of heart disease.

Nausea, which is usually mild and transient, is the most common side effect of SSRIs

Meta-analyses suggest that patients are more likely to discontinue taking tricyclics than SSRIs.[8] Adherence to antidepressant medications by older patients has been associated with lower perceived stigma of mental illness, higher self-rated severity of illness, age over 60, and absence of a personality disorder.[9]

SSRI side effects

The most common side effect of SSRIs is nausea, which is usually mild and occurs in the first weeks of treatment.[2] Dry mouth is related to noradrenergic influences on the salivary gland. Anxiety is usually transient.

Sedation can be a problem in older patients who use SSRIs. Among the six SSRIs indicated for depression, paroxetine appears to be the most sedating.[10] Paroxetine exhibits the most muscarinic blockade in vitro, with a binding affinity less than

Table 2

CYTOCHROME P450 ISOZYMES INHIBITED BY SSRI ANTIDEPRESSANTS (IN VITRO)

Drug	1A2	2C9	2C19	2D6	3A4
Fluoxetine	+	++	+	+++	++
Sertraline	+	+	+	+	+
Paroxetine	+	+	+	+++	+
Citalopram	+	○	○	+	○
Escitalopram	○	○	○	○	○
Fluvoxamine	+++	++	+++	+	++

Source: Adapted from Greenblatt et al. *J Clin Psychiatry* 1998;59(suppl 15):19-27, and von Moltke et al. *Drug Metab Dispos* 2001;29:1102-9.

that of imipramine but greater than nortriptyline.[11] Studies in older patients have suggested, however, that cognitive function is not compromised with paroxetine, as is observed with other antidepressants with anticholinergic action.[6]

Sexual function can be diminished by SSRIs; the most common sexual side effects are anorgasmia and delayed orgasm.[12] Preserving sexual function is important to many older men and women who retain their interest in sexual activity well into later life.

Withdrawal syndrome. Abrupt discontinuation of some SSRIs can lead to withdrawal side effects, such as dizziness, fatigue, and nausea. In a study of young and older adults, withdrawal syndrome followed abrupt discontinuation at rates of 14% with fluoxetine and 60% with sertraline or paroxetine.[13]

Abrupt discontinuation of some SSRIs can lead to withdrawal side effects

Elimination half-life. Medication half-lives tend to be prolonged in older patients because of age-related pharmacokinetic changes. SSRIs with relatively shorter half-lives—such as citalopram, sertraline, paroxetine, and fluvoxamine—could be eliminated fairly rapidly should adverse events arise.

On the other hand, use of a longer-acting agent, such as fluoxetine, may be an advantage if compliance is a problem. In this case, fluoxetine's prolonged washout rate could help protect a patient from relapse, even when doses are missed.

Potential drug-drug interactions

Individual SSRIs have different effects on the cytochrome P450 system (*Table 2*).[14,15] For example, fluoxetine, sertraline, and paroxetine—but not fluvoxamine—are in vitro inhibitors of the 2D6 isoenzyme system,[16] which metabolizes TCAs, type Ic antiarrhythmics, alpha-adrenergic blockers, dextromethorphan, chemotherapeutic agents, and some antipsychotics. Citalopram has minimal inhibitory activity and escitalopram has virtually no inhibitory action on CYP 2D6.[17]

Cytochrome P450 3A4 metabolizes numerous drugs, including alprazolam, triazolam, carbamazepine, calcium channel blockers, and others. The 3A4 enzymes are inhibited by fluoxetine, sertraline, and fluvoxamine.[18]

Cytochrome P450 1A2 is the liver isoenzyme responsible for dealkylating theophylline, caffeine, and phenacetin. This enzyme system also metabolizes tacrine and clozapine. Of the SSRIs, fluvoxamine is the most potent inhibitor of the 1A2 enzyme, while escitalopram is a negligible inhibitor.[17]

Cytochrome P450 2C is a subfamily of isoenzymes that includes 2C9, 2C10, 2C19, and others. This system metabolizes some antidepressants as well as warfarin, phenytoin, and diazepam. Inhibitors of this system include fluvoxamine, fluoxetine, sertraline, and paroxetine.[18]

Related resources

- National Institute of Mental Health. Older adults: Depression and suicide facts. www.nimh.nih.gov/publicat/elderlydepsuicide.cfm
- WebMD Health/depression. http://my.webmd.com/condition_center/dep
- Salzman C, Wong E, Wright BC. Drug and ECT treatment of depression in the elderly, 1996-2001: a literature review. *Biol Psychiatry* 2002;52(3):265-84.

DRUG BRAND NAMES

Alprazolam • Xanax
Citalopram • Celexa
Clozapine • Clozaril
Diazepam • Valium
Escitalopram • Lexapro
Fluoxetine • Prozac
Fluvoxamine • Luvox
Paroxetine • Paxil
Sertraline • Zoloft
Tacrine • Cognex
Triazolam • Halcion

DISCLOSURE

Dr. Kasckow reports that he receives grant/research support from, serves as a consultant to, or is on the speakers bureau of Eli Lilly and Co., Forest Laboratories, Pharmacia Corp., Solvay Pharmaceuticals, AstraZeneca Pharmaceuticals, Organon, Janssen Pharmaceutica, and Pfizer Inc.

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MAO inhibitors. Concomitant use of serotonin-acting drugs and monoamine oxidase inhibitors should be avoided. When used in combination, SSRIs and MAO inhibitors can cause a serotonin syndrome, with potential hyperpyretic crises, seizures, coma, and death. When switching medications, it is important to eliminate any serotonin-acting drug before starting an MAO inhibitor.[2]

In young adults, a 7-day washout is needed when switching from fluvoxamine and 14 days when switching from sertraline, citalopram, or paroxetine. With fluoxetine, the washout period is 35 days in young adults. Because medication half-lives in older patients may be prolonged two- to three-fold, it is advisable to proceed conservatively and extend these washout periods accordingly.

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Bottom Line

When geriatric depression is recognized, it usually responds favorably to treatment, although aggressive intervention may be required. SSRIs are as effective as tricyclics but offer a side-effect profile that is more easily tolerated by older patients.