

Late-life depression

People aged 65+ account for relatively high number of suicide deaths

By Feng Chang, BScPhm, PharmD

Late-life depression is an important health issue. According to US data, the prevalence of clinically significant depressive symptoms ranges from 8% to 15% among community-dwelling elderly persons and is about 30% among the institutionalized elderly.¹⁻⁴ Depression affects an estimated 200,000 people over the age of 65 in Canada.⁵ Groups at particular risk include in-patients, long-term care residents, and patients with dementia.⁶ With an anticipated increase in the geriatric population as the baby boomer generation ages, it is important for health care professionals to become familiar with the recognition of the disease and its treatment.

Etiology

The exact etiology of depression remains largely unknown. Theories based on neurotransmitters point to abnormal levels of norepinephrine, serotonin, and dopamine. Research has shown that the time spent depressed is related to reduced hippocampal volume, which could indicate that depression is neurotoxic.⁷ Antidepressants can stimulate brain-derived neurotrophic factor production and reverse this process,⁸ and this improved ability to form new neurons, or neurogenesis, is seen with various types of antidepressants.⁹ These discoveries suggest that medical interventions should start early; appropriate treatment duration and adherence will be important for ensuring positive patient outcomes.

Assessment

Diagnosis of depression is itself a challenge. Depression can profoundly impair a person's ability to function, regardless of his or her age.¹⁰ Unfortunately, older patients and health care providers alike may view decreased func-

Optimizing therapy

Pharmacists can help to optimize therapy by assisting the physician with antidepressant selection, dose titration, drug-interaction checking, monitoring adherence, and patient education.

Pharmacists can also improve adherence by helping patients manage side effects, identifying possible drug interactions or potential drug-related problems associated with sedative medications (such as falls), and providing ongoing support.

tioning as a natural consequence of aging and/or concurrent physical illness rather than as a symptom of depression.³

Depressed older patients often present with atypical symptoms, such as anxiety, irritability, delusions (instead of suicidal thoughts), sadness, or feelings of depression.^{5,11-13} Patients may also appear disoriented, apathetic, and unreactive, and may experience loss of appetite, insomnia, incontinence, or memory problems. Other symptoms to watch for include paranoia, feelings of guilt or sinfulness, and thoughts focused on losses in life, such as people or money.

Standard questionnaires used for diagnosis include the Geriatric Depression Scale (GDS) and the Even Briefer Assessment Scale for Depression (EBAS DEP)¹⁴⁻¹⁵; the Cornell Scale for Depression in Dementia is useful for distinguishing cognitive symptoms from dementia.¹⁶ Familiarity with these scales will help pharmacists know what to look for and how to engage in information-gathering conversations with patients or caregivers. See box below for common risk factors for depression.^{12,17}

Treatment goals

The goals of treatment for late-life depression include

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COMMON RISK FACTORS FOR DEPRESSION

- Prior history of depression
- Poor self-rated health
- Poor functional capacity
- Loss of a spouse
- Social isolation/loneliness
- Chronic medical conditions (anxiety disorders, substance abuse, myocardial infarction, stroke, Parkinson's disease, dementia)
- Perceived negative changes in life

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relieving target symptoms, restoring functional ability, and preventing recurrence.

Non-pharmacological therapies

Psychotherapy

Integrated cognitive, behavioural, or interpersonal psychotherapies are useful when patients are dealing with acute stress or cannot tolerate medications. For isolated elderly patients, this may provide a comforting, safe environment for social interaction, but it is not recommended as monotherapy in severe depression.¹ In the elderly, unwillingness to see a therapist, physical barriers to getting to appointments, and the expense involved can be deterring factors.

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is safe, effective, and well tolerated in late-life depression.¹⁸⁻¹⁹ It is useful in patients with psychotic symptoms or severe melancholy, or in patients who do not respond to medications. Adverse effects include amnesia during ECT and headaches. The relapse rate is high, so patients who respond to ECT can benefit from maintenance antidepressant therapy and/or maintenance ECT.

Pharmacotherapy

Antidepressants are the mainstay of therapy in late-life depression. Physiological changes with age affect pharmacokinetics. Reduced stature, decreased drug metabolism and elimination rates put older patients at greater risk for medication toxicity due to increased drug concentration and longer half-life. The elderly are also more sensitive to side effects, more likely to have organ damage and/or concomitant illnesses, and more at risk for drug interactions due to polypharmacy.

Sensory impairment (loss of hearing, sight, or dexterity) or cognitive impairment (memory impairment, dementia) can be barriers to adherence. All of these issues need to be considered when choosing an antidepressant. Medication should be selected based on individual response, tolerability, drug interactions, comorbidity, and adherence. Start

First-line treatments	Mirtazapine, citalopram, venlafaxine, bupropion, fluvoxamine, paroxetine, sertraline, moclobemide
Second-line treatments	Fluoxetine, nortriptyline, desipramine, trazodone
Third-line treatments	Amitriptyline, imipramine, clomipramine, doxepin, maprotiline, phenelzine, tranylcypromine
Maintenance-phase treatment	Two years

Antidepressant	Starting dose	Usual maintenance dose
Mirtazapine	7.5 mg at bedtime, increase to 15 mg after one week	30 mg at bedtime
Citalopram	10 mg daily	20 mg daily
Venlafaxine	37.5 mg daily	75–150 mg daily

the dose low — at half the normal adult dose for most agents — and slowly titrate up. Allow up to twice as long (8–12 weeks) to assess response.²⁰ Prolonged use of benzodiazepines in patients with symptoms of agitation or anxiety is not appropriate.

Recommended antidepressants and dosing for the elderly are listed in Tables 1 and 2 as per Canadian Psychiatric Association guidelines. Table 3 discusses all the antidepressants in more detail by class of action.

Selective serotonin reuptake inhibitors

Commonly used as first-line agents, selective serotonin reuptake inhibitors (SSRIs) increase serotonin concentration in the brain. They have the advantage of good efficacy, minimal anticholinergic effects, and once-daily dosing.

Side effects include somnolence, insomnia, gastrointestinal (GI) symptoms, serotonin syndrome, and sexual dysfunction. Of this class, citalopram has an earlier onset of action and fewer GI side effects, and it causes less anxiety.²¹ Fluvoxamine causes nausea and could elevate the international normalized ratio (INR) if taken together with warfarin. Paroxetine, sertraline, and fluoxetine are associated with more drug interactions due to inhibition of cytochrome P450 (CYP) enzymes. The long elimination half-lives of fluoxetine and its active metabolite norfluoxetine (up to 16 days) also make it the least desirable of the class.

Noradrenergic/specific serotonergic antidepressants

The noradrenergic/specific serotonergic antidepressant (NaSSA) mirtazapine has a dual action, increasing noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT₁ receptors. This specificity leads to reduced anxiety, restlessness, insomnia, and GI side effects with NaSSAs compared to SSRIs.²²⁻²⁴ Mirtazapine also has a shorter time to response, at two weeks, compared to paroxetine.²⁴ Sedation, increased appetite, and weight gain may occur. Patients should be reminded to take mirtazapine at bedtime.

Serotonin norepinephrine reuptake inhibitors

Venlafaxine, a serotonin norepinephrine reuptake inhibitor

TABLE 3 — Side-effect profile and dosing for classes of antidepressants

Medication	Side-effect profile			Dosing (mg/day)	Additional comments
	AC	S	OH		
Nonselective cyclic antidepressants					
Amitriptyline	++++	++++	++	50–300	<ul style="list-style-type: none"> • Desipramine and nortriptyline are preferred over others • Can be useful in depression associated with anxiety/sleep disturbance • Use low doses if used in combination with SSRIs, as CYP 2D6 inhibition will reduce TCA metabolism
Imipramine ¹	+++	++++	+++	30–300	
Doxepin	++	+++	++	25–300	
Desipramine	+	+	+	10–300	
Nortriptyline	++	++	+	10–100	
Maprotiline	++	++	+	50–225	
Monoamine oxidase inhibitors, irreversible and reversible (MAOIs/RIMAs)					
Tranylcypromine	+	+	0	30–60	<ul style="list-style-type: none"> • Can lead to fatal hypertensive crisis • Can be useful for atypical depression at higher doses • Allow 14 days between switching MAOIs/SSRIs/TCAs; allow five weeks if switching from fluoxetine to MAOI
Phenelzine	+	+	+	45–90	
Moclobemide (RIMA)	+	0	+	100 bid, up to 600–900/day	<ul style="list-style-type: none"> • Can be useful in TCA-resistant patients, atypical patients, comorbid anxiety • Give after meals
Selective serotonin reuptake inhibitors (SSRIs)					
Citalopram	0/+	0/+	0/+	20–60	<ul style="list-style-type: none"> • Not affected by food • Potential drug interactions with inhibition of CYP enzymes; commonly affected drugs include theophylline, warfarin, phenytoin, carbamazepine, clarithromycin, benzodiazepines, TCAs • Citalopram has the least risk for CYP drug interactions
Fluoxetine	0/+	0/+	0/+	20–80	
Fluvoxamine	0/+	0/+	0	50–300	
Paroxetine	0	0/+	0	10–50	
Sertraline	0	0/+	0	50–200	
Serotonin-2a antagonists/reuptake inhibitors (SARIs)					
Trazodone	+	++++	++	150–600	<ul style="list-style-type: none"> • Take at bedtime (sedation) • Not recommended during initial recovery phase of myocardial infarction (arrhythmogenic)
Norepinephrine dopamine reuptake inhibitors (NDRIs)					
Bupropion	+	++	+	200–450	<ul style="list-style-type: none"> • Divide dose as bid • Increased seizure risk
Serotonin norepinephrine reuptake inhibitors (SNRIs)					
Venlafaxine	0	0	0	75–375	<ul style="list-style-type: none"> • Lower doses seem to improve attention, concentration, memory, and fine-motor ability
Noradrenergic/specific serotonergic antidepressants (NaSSA)					
Mirtazapine	++	+++	++	15–45	<ul style="list-style-type: none"> • Anti-anxiety effects, improves sleep disorders • Monitor weight gain in patients already overweight or obese • Rare cases of agranulocytosis/neutropenia; monitor for signs of infection
0 → ++++ = least effect to most effect. TCA= tricyclic antidepressants; AC= anticholinergic; S= sedation; OH= orthostatic hypotension; CYP= cytochrome P450.					

(SNRI), has action on both serotonin and norepinephrine. It has been shown to produce higher remission rates than SSRIs.²⁵ It is well absorbed and well tolerated, and the extended-release (XR) formulation has a half-life of about 24 hours, allowing for once-daily administration. A recent meta-analysis found it to be more effective than SSRIs and superior to imipramine.²⁶ Venlafaxine is associated with a dose-dependent increase in diastolic blood pressure, and like SSRIs, it carries the risk of serotonin syndrome and sexual dysfunction.

Reversible monoamine oxidase inhibitors

Moclobemide, a reversible inhibitor of monoamine oxidase (RIMA), selectively and reversibly blocks the action of monoamine oxidase A (MAO-A), which is responsible for breaking down neurotransmitters. There is less concern associated with tyramine and food restrictions with moclobemide than with irreversible monoamine oxidase inhibitors (MAOIs) (see Other Antidepressants, below) because the MAO-A blockade is reversible, but patients should still be informed to take moclobemide after tyramine-rich meals to minimize the risk.²⁷ Food restrictions are still recommended for high doses or for hypertensive patients. Moclobemide has minimal anticholinergic effects. It is also associated with fewer GI effects and less sexual dysfunction than SSRIs.²⁸

Norepinephrine dopamine reuptake inhibitors

Bupropion, a norepinephrine dopamine reuptake inhibitor (NDRI), blocks the neuronal uptake of dopamine and norepinephrine with negligible effects on serotonin. This different mechanism is advantageous for patients who do not respond to or cannot tolerate the serotonergic agents. Incidence of sexual dysfunction is low. It is available in a slow-release formulation for convenient dosing and improved tolerability. In the elderly, it can also improve focus and attention.¹² One disadvantage with bupropion is the increased risk of seizures (4/1000 in doses up to 450 mg/day).²⁹ This incidence of seizures could exceed that of other marketed antidepressants by as much as four-fold.³⁰

Other antidepressants

Older antidepressants such as the tricyclic antidepressants (TCAs) (amitriptyline, imipramine, doxepin), tetracyclics (amoxapine and maprotiline), and the irreversible MAOIs (phenelzine, tranylcypromine) are not recommended in the elderly.

The cyclic antidepressants have strong anticholinergic effects (dry mouth, blurred vision, orthostatic hypotension, constipation, memory impairment, tachycardia) and are not recommended in patients with urinary retention, glaucoma, or ischemic heart disease.³¹⁻³² They also increase the risk of falls and hip fractures in the elderly.³³

MAOIs are associated with potentially fatal hypertensive crisis when taken with certain drugs or tyramine-containing foods; patients taking them need to follow dietary

restrictions and have drug interactions carefully monitored. MAOIs also cause orthostatic hypotension, which is a risk factor for falls in the elderly.

Nortriptyline and desipramine are the preferred agents among the nonselective cyclic antidepressants, mostly because of their comparatively favourable side effect profile. Desipramine is less sedating and has the lowest anticholinergic profile.³⁰ Nortriptyline has a lower incidence of orthostatic hypotension. Trazodone has the drawback of heavy sedation through histamine receptor blockade, so its use is limited; lower doses at bedtime can be used to increase REM sleep.

Over-the-counter supplements

St. John's wort, or hypericin, has been used for more than 15 years as a natural remedy for depression. Its mechanism of action is not completely understood, but it appears to modulate the effects of serotonin, dopamine, and norepinephrine, possibly through reuptake inhibition.³⁴ In clinical studies, it has shown comparable efficacy to other antidepressants in mild to moderate depression. However, it is not indicated for severe depression.³⁵ St. John's wort interacts with a number of drugs, including SSRIs, MAOIs, indinavir, cyclosporine, digoxin, warfarin, and estrogen.³⁴ When used orally in large doses, St. John's wort can lead to severe phototoxic skin reactions.

There is some evidence that 5-hydroxytryptophan (5-HTP) is comparable to fluvoxamine and imipramine.³⁶⁻³⁷ It seems to improve symptoms of depression, including in patients with treatment-resistant depression.^{36,38} The mechanism of action is related to both L-tryptophan and serotonin. In the body, L-tryptophan is converted to 5-HTP, which is then converted to serotonin. 5-HTP side effects are mostly GI-related: heartburn, nausea, vomiting, abdominal pain, and anorexia. Drug interactions could occur with carbidopa, SSRIs, TCAs, and MAOIs.

Many other over-the-counter (OTC) supplements are advertised for depression, including S-adenosylmethionine (SAME), fish oil, vitamin B, and trace minerals. Pharmacists should take the time to discuss the benefits and risks of these with their patients. OTC supplements may not have clearly marked labels or strict quality control measures, so their safety and efficacy cannot always be guaranteed. Patients should be encouraged to see a qualified health professional before taking any of these supplements.

Management strategies

Pharmacists are in a unique position to help monitor the patient's progress once an antidepressant is selected. It is important that they educate patients about the onset and duration of the medication and remind them not to discontinue therapy abruptly, especially if they begin to feel better, because discontinuation syndrome (insomnia, nausea, imbalance, hyperarousal, flu-like symptoms) can occur. Citalopram, mirtazapine, and bupropion are associated with less risk for this syndrome.³⁹ Issues with intoler-

ance can be dealt with by adjusting administration times or lowering or splitting the dose. If a single agent causes intolerable side effects at full dose, it is possible to use two agents, both at partial doses. Suggesting OTC agents for symptom control, such as using dimenhydrinate for nausea, can be helpful if the antidepressant is otherwise effective.

If a patient is compliant and tolerating the medication but response does not seem adequate, the dose should be increased to the higher end of the dosing range before considering it a treatment failure. If a patient is intolerant or has no response after an appropriate course, another agent can be recommended. A switch can be made to any of the first-line agents recommended for the elderly (Table 1). Among SSRIs, the response rate is 66% after switching to a second SSRI when the first SSRI is poorly tolerated and 48% when the patient is refractory to the first agent.²⁵ First-line agents should be tried before moving to other agents.

If a patient has a partial response after an appropriate course, augmentation with lithium, liothyronine, stimulants (amphetamine, methylphenidate), atypical antipsychotics such as risperidone, or folic acid may produce additional benefit. If choosing to use combination therapy, recommend two agents with different mechanisms of action. Remind the patient that it will take another four to six weeks for improvement after the initiation of a combination. Mirtazapine and SSRIs, bupropion and SSRIs, and TCAs and SSRIs are combinations that can lead to more rapid onset, higher response rate, or reduced side effects.⁴⁰ Keep in mind there is added risk of toxicities and drug-drug interactions with combination therapy. Adherence can also become an issue.

Maintenance therapy

The acute phase of major depression lasts at least 8–12 weeks in the elderly.⁴¹ If the patient's symptoms lessen during this time and previous level of functioning returns, the medication should be continued for at least six months and then reassessed. The Canadian Psychiatric Association recommends two years as maintenance, since recurrence of symptoms can occur in up to 50% of patients within the first two years.^{19,42} Grieving-related depression generally

lasts at least one year. Patients who have had three or more episodes of major depression or two episodes followed by rapid recurrence, patients who were older at onset of depression (> 60 years), and patients with a family history of mood disorders may need maintenance therapy indefinitely.⁴³

Suicide prevention

Depression is a predictor for suicide. People 65 and over account for a disproportionately high number of suicide deaths when compared to other age groups.^{5,44-45} The elderly are less likely than younger patients to seek or respond to help for the prevention of suicide.¹ As front-line health care professionals, pharmacists need to be on the alert for signs of depression and suicidal ideation. Look for clues, including statements such as "feeling empty," "feeling like no one loves me," or "feeling like life is not worth living"; fatigue; guilt; feelings of worthlessness; and unusual sleeping or eating habits.⁵ Antidepressants that are easily toxic in overdose, such as the TCAs, should be prescribed in small quantities, and the patient should be monitored closely while receiving them.

Conclusion

Late-life depression is a debilitating illness. Pharmacists have the opportunity to interact with older patients on a regular basis and can help improve the health and quality of life of these patients. As medication experts, pharmacists can help to optimize the patient's therapy by assisting the physician with antidepressant selection, dose titration, drug-interaction checking, adherence monitoring, and patient education.

Pharmacists can also help improve adherence by helping patients manage side effects, identifying potential drug-related problems associated with sedative medications (such as falls), and providing ongoing support. They should encourage the patient or caregiver to discuss any concerns or unusual effects. For many community-dwelling elderly patients, access to and trust in their pharmacist will facilitate their road to recovery from depression. ■

REFERENCES

1. Blazer D. Depression. In: Beers MH, Berkow R, eds. *Merck manual of geriatrics*. Whitehouse Station, NJ: Merck and Co., Inc.; 2000:310-22.
2. Blazer D, Swartz M, Woodbury M, et al. Depressive symptoms and depressive diagnoses in a community population. Use of a new procedure for analysis of psychiatric classification. *Arch Gen Psychiatry* 1988;45:1078-84.
3. NIH consensus conference. Diagnosis and treatment of depression in late life. *JAMA* 1992;268:1018-24.
4. Lebowitz BD, Pearson JL, Schneider LS, et al. Diagnosis and treatment of depression in late life. Consensus statement update. *JAMA* 1997;278:1186-90.
5. Older adults: depression and suicide facts (2003). National Institute of Mental Health website. Available: www.nimh.nih.gov/publicat/elderlydepsuicide.cfm (accessed January 5, 2005.)
6. Bruce ML, McNamara R. Psychiatric status among the homebound elderly: an epidemiologic perspective. *J Am Geriatr Soc* 1992;40:561-6.
7. Sheline YI, Sanghavi M, Mintun MA, et al. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci* 1999;19:5034-43.
8. Stahl S. *Essential psychopharmacology: neuroscientific basis and practical applications*. New York, NY: Cambridge University Press; 2000.
9. Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. *Arch Gen Psychiatry* 1997;54:597-606.
10. *Clinical Practice Guideline Number 5: Depression in Primary Care, 1: Detection and Diagnosis*. Rockville, MD: Agency for Health Care

References cont'd on p. 36

- Policy and Research, US Department of Health and Human Services; 1993. AHCPR Publication No. 93-0550.
11. Depression in special circumstances: the elderly. Canadian Network for Mood and Anxiety Treatments website. Available: www.canmat.org/depress/index.html (accessed December 8, 2004.)
 12. Sable JA, Dunn LB, Zisook S. Late-life depression. How to identify its symptoms and provide effective treatment. *Geriatrics* 2002;57:18-9, 22-3, 26.
 13. Alexopoulos GS, Katz IR, Reynolds CF, Ross R. *Depression in older adults: a guide for patients and families*. White Plains, NY: Expert Knowledge Systems and Comprehensive Neuroscience Inc.; 2001.
 14. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatry Res* 1983;17:37-49.
 15. Allen N, Ames D, Ashby D, et al. A brief sensitive screening instrument for depression in late life. *Age Ageing* 1994;23:213-9.
 16. Alexopoulos GS, Abrams RC, Young RC, et al. Cornell scale for depression in dementia. *Biol Psychiatry* 1988;23:271-84.
 17. Doraiswamy PM. Contemporary management of comorbid anxiety and depression in geriatric patients. *J Clin Psychiatry* 2001;62(suppl 12):30-5.
 18. Mulsant BH, Rosen J, Thornton JE, et al. A prospective naturalistic study of electroconvulsive therapy in late-life depression. *J Geriatr Psychiatry Neurol* 1991;4:3-13.
 19. Thorpe L, Whitney DK, Kutcher SP, et al. Clinical guidelines for the treatment of depressive disorders. VI. Special populations. *Can J Psychiatry* 2001;46(suppl 1):63S-76S.
 20. Thomas L, Mulsant BH, Solano FX, et al. Response speed and rate of remission in primary and specialty care of elderly patients with depression. *Am J Geriatr Psychiatry* 2002;10:583-91.
 21. Stahl SM. Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. *Biol Psychiatry* 2000;48:894-901.
 22. De Boer T. The pharmacologic profile of mirtazapine. *J Clin Psychiatry* 1996;57(suppl 4):19-25.
 23. Fawcett J, Barkin RL. Review of the results from clinical studies on the efficacy, safety and tolerability of mirtazapine for the treatment of patients with major depression. *J Affect Disord* 1998;51:267-85.
 24. Schatzberg AF, Kremer C, Rodrigues HE, et al., Mirtazapine vs Paroxetine Study Group. Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. *Am J Geriatr Psychiatry* 2002;10:541-50.
 25. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry* 2001;178:234-41.
 26. Smith D, Dempster C, Glanville J, et al. Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. *Br J Psychiatry* 2002;180:396-404.
 27. Fitton A, Faulds D, Goa KL. Moclobemide: a review of its pharmacological properties and therapeutic use in depressive illness. *Drugs* 1992;43:561-96.
 28. Amrein R, Stabl M, Henauer S, et al. Efficacy and tolerability of moclobemide in comparison with placebo, tricyclic antidepressants, and selective serotonin reuptake inhibitors in elderly depressed patients: a clinical overview. *Can J Psychiatry* 1997;42:1043-50.
 29. Wellbutrin [product information]. Research Triangle Park, NC: Glaxo Wellcome Inc; 2002.
 30. Hebel SK, Killion KH, Burnham TH, et al., eds. *Drug Facts and Comparisons 2003 Pocket Version*. St. Louis, MO: Facts and Comparisons; 2002.
 31. McLeod PJ, Huang AR, Tamblyn RM, et al. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. *CMAJ* 1997;156:385-91.
 32. Roose SP, Laghrissi-Thode F, Kennedy JS, et al. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. *JAMA* 1998;279:287-91.
 33. Ray WA, Griffin MR, Schaffner W, et al. Psychotropic drug use and the risk of hip fracture. *N Engl J Med* 1987;316:363-9.
 34. St. John's Wort. Natural Medicines Comprehensive Database. Available: www.naturaldatabase.com (accessed December 8, 2004.)
 35. Philipp M, Kohnen R, Hiller KO. Hypericum extract versus imipramine or placebo in patients with moderate depression: randomised multicentre study of treatment for eight weeks. *BMJ* 1999;319:1534-8.
 36. Coppen A, Whybrow PC, Noguera R, et al. The comparative antidepressant value of L-tryptophan and imipramine with and without attempted potentiation by liothyronine. *Arch Gen Psychiatry* 1972;26:234-41.
 37. Poldinger W, Calanchini B, Schwarz W. A functional-dimensional approach to depression: serotonin deficiency as a target syndrome in a comparison of 5-hydroxytryptophan and fluvoxamine. *Psychopathology* 1991;24:53-81.
 38. Nakajima T, Kudo Y, Kaneko Z. Clinical evaluation of 5-hydroxy-L-tryptophan as an antidepressant drug. *Folia Psychiatr Neurol Jpn* 1978;32:223-30.
 39. Reesal R. Antidepressant discontinuation syndrome. *Can J Diagnosis* 1999;Nov:9-125.
 40. Fava M. Augmentation and combination strategies in treatment-resistant depression. *J Clin Psychiatry* 2001;62(suppl 18):4-11.
 41. Georgotas A, McRue RE. The additional benefit of extending an antidepressant trial past seven weeks in the depressed elderly. *Int J Geriatr Psychiatry* 1989;4:191-5.
 42. Feinberg M, Dinwiddie J, Wells BG. Depression in the elderly. *J Am Soc Consult Pharm* 1997;12(Suppl 4):12-1 to 10.
 43. Hirschfeld RMA. Guidelines for the long-term treatment of depression. *J Clin Psychiatry* 1994;55(suppl 12):60-9.
 44. Penninx BW, Geerlings SW, Deeg DJ, et al. Minor and major depression and the risk of death in older persons. *Arch Gen Psychiatry* 1999;56:889-95.
 45. Schulz R, Beach SR, Ives DG, et al. Association between depression and mortality in older adults, the cardiovascular health study. *Arch Intern Med* 2000;160:1761-8.