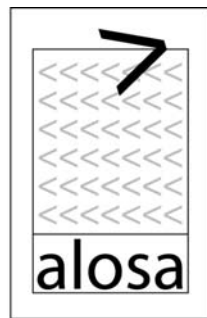


The Pursuit of Happiness: Management of Depression in the Elderly

A review for the practicing physician



The Alosa Foundation



Balanced data about medications

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Introduction

By 2020 depression will be second only to heart disease as a cause of disability and premature death in the developed world.¹ Depressive symptoms in the elderly are associated with reduced physical performance and functional status,² a greater risk of nursing home admission,³ increased health care utilization, and higher health care costs.⁴ Untreated depression can delay recovery or worsen outcomes of other illnesses and increase mortality.^{5, 6} Suicide rates are highest in the elderly, particularly in white elderly males. Seniors are 33% more likely to commit suicide than the general population.⁷

Despite a high prevalence and substantial associated morbidity, depression is under-recognized and inadequately treated in the elderly. A major reason for this is that patients, families, and physicians often incorrectly believe that depressive symptoms are an expected part of normal aging.⁸ The diagnosis of depression can be particularly challenging in the elderly as older adults may present differently than do younger adults.

Seniors are 33% more likely to commit suicide than the general population.

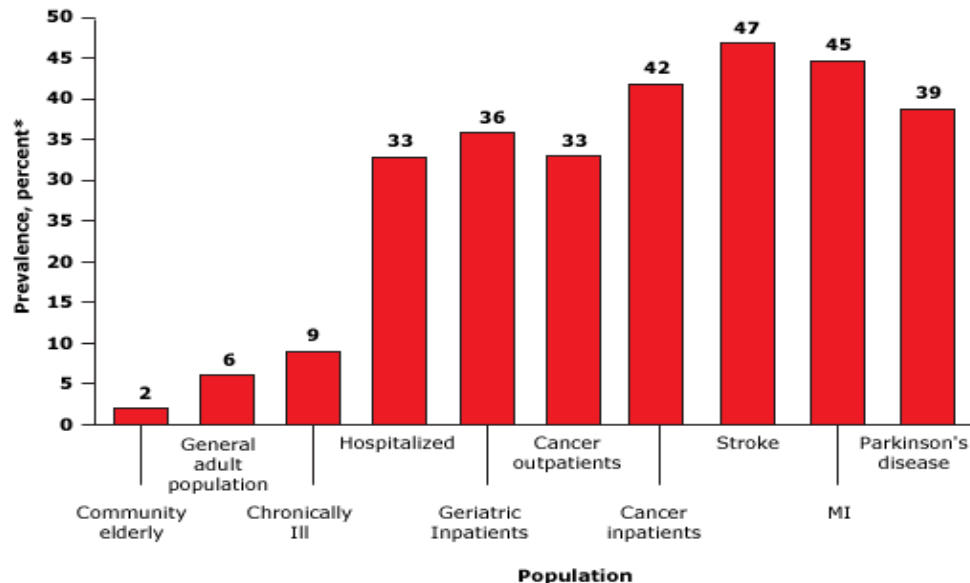
Nevertheless, prompt recognition and proper management of depression can alleviate symptoms, as older adults can benefit substantially from both medication and non-pharmacologic interventions. Prescribing in the elderly can be difficult, and the presence of comorbid conditions, functional limitations, and cognitive disorders make adverse drug reactions more likely. Elderly patients are at high risk of adverse effects stemming from over-diagnosis of depression and the unnecessary use of psychoactive medications; therefore, making appropriate treatment decisions is extremely important.

This document provides the practicing physician with an overview of depression in the community dwelling elderly. We present guidance on how to diagnose major depression, and how to distinguish patients with major depression from those with less severe symptoms. We review the appropriate management, both pharmacologic and non-pharmacologic, of depressed patients. We then identify indications for medication therapy, how to choose the appropriate drug for elderly patients if one is needed, and how to manage patients after therapy is initiated.

Epidemiology of depression in the elderly

Depression is the most common psychiatric disorder among the elderly. The prevalence of major depression ranges from 1% to 4% in those over age 65 but rises to over 13% in those who require home health care and 11% in elderly hospitalized patients.⁹ However, an estimated 5 million elderly have “subsyndromal” depression, a condition that falls short of meeting the full diagnostic criteria and is sometimes called minor depression.¹⁰ Subsyndromal depression is associated with an increased risk of developing major depression.¹¹ The prevalence of depression is expected to increase as the population of older Americans grows.

Figure 1: Prevalence of major depression in the elderly¹²



The direct and indirect healthcare costs attributable to depression are massive – estimated at over \$83.1 billion for the U.S. in 2000.¹³ Of that total, \$26.1 billion were direct medical costs, \$5.4 billion were suicide-related mortality costs, and \$51.5 billion were workplace costs. Mental health care has been progressively moving into the outpatient setting, and medications have become the preferred mode of therapy for most patients. Compared to costs for depression in 1990, there was a 33% decrease in spending on inpatient care, with a 47% increase in outpatient care costs and a 453% increase in drug costs.¹³ In 2007, U.S. spending on antidepressant medications was approximately \$12 billion.¹⁴

Diagnosis

Diagnosing depression in the elderly

Depression should be distinguished from commonplace unhappiness or grieving, which are normal parts of the human experience. The diagnosis of depression in older patients can be particularly difficult because depressive symptoms may complicate or co-exist with chronic medical conditions such as heart disease, stroke, diabetes, and Parkinson's disease.¹⁵⁻¹⁷ Major depression may also be a prodrome of dementia or may develop after the onset of cognitive decline.^{18, 19}

Depressed mood and decreased pleasure from the activities of life are the hallmarks of depression.

The most important hallmarks of depression are depressed mood and decreased pleasure from activities of life. However, in older depressed patients the prominent presenting complaints may be fatigue, poor sleep, low appetite, anxiety, memory loss or cognitive decline, rather than the cardinal features of lowered mood and loss of interest in activities.²⁰ Other elderly depressed patients may present with pain, hypochondriasis, or pseudodementia.²¹

Depressive disorders often lead to suicide in older adults. Up to 75% of those who committed suicide had seen their health care providers within the month before their death.²² Yet clinicians frequently fail to discuss suicidality with the elderly, and are 94% less likely to ask about suicidal thoughts in this population, even though they are at such high risk of self-harm.²³ Primary care physicians can play a critical role in preventing death and disability by making an early diagnosis of depression and initiating treatment or referral. Thus, it is important for the primary care provider to perform an adequate workup, including a discussion about mood symptoms.

Up to 75% of those who committed suicide had seen their health care providers within the month before their death.

The management of depression depends on applying the correct criteria to make an accurate diagnosis. Fortunately, there are well validated brief screening tools that can begin to assess whether patients meet criteria for major depression, or whether their symptoms represent dysthymia or other less severe disorders. Given the concern for suicide described above, an assessment for safety should be part of every evaluation. Making the diagnosis systematically and correctly is the first step toward formulating an effective treatment approach.

Major depression

Major depression is a severe, life-threatening diagnosis that can be as important to identify as pneumonia or cancer. And like pneumonia and cancer, if the diagnosis is made accurately and in a timely way, a potentially devastating illness can be identified and often successfully treated. The specific criteria for major depression require the existence of at least one **major depressive episode**. Its symptoms must be present every day for at least 2 weeks, represent a change from the patient's baseline, and cause significant distress or impairment in functioning.

In addition, at least one of two core symptoms must be present: **anhedonia** and/or **depressed mood**. Patients who meet these criteria must also experience at least 3 additional symptoms listed in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV),²⁴ including weight loss or gain, change in sleep patterns, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, poor concentration, and thoughts of death (see table below).

Although a depressive episode is defined as lasting at least two weeks, patients who have not been treated may have symptoms of major depression for much longer. While 70-80% of such patients will eventually have a full remission from major depression, a substantial minority (20-25%) will have only partial remission. **In 5-10% of patients the symptoms of major depression will persist for 2 or more years; this condition is defined as chronic major depressive disorder.**

Major Depressive Episode (DSM-IV TR) *

Either 1 or 2 of the following must be present

- **depressed mood** most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)
- **markedly diminished interest or pleasure** in all or almost all activities most of the day, nearly every day (as indicated by either subjective account or observation made by others; also called “anhedonia”)

Plus other symptoms to make a total of 5

- **significant weight gain or loss (when not dieting)** more than 5% of body weight in a month, or **decrease or increase in appetite** nearly every day
- **insomnia or hypersomnia** nearly every day
- **psychomotor agitation or retardation** nearly every day, observable by others, not merely subjective feelings of restlessness or being slowed down
- **fatigue or loss of energy** nearly every day
- **feelings of worthlessness or excessive or inappropriate guilt**, may be delusional, occurring nearly every day (i.e., not merely self-reproach or guilt about being sick)
- **indecisiveness or diminished ability to think or concentrate** nearly every day (either by subjective account or as observed by others)
- **recurrent thoughts of death** (not just fear of dying), **recurrent suicidal ideation** even without a specific plan, or a **suicide attempt or a specific plan** for committing suicide

In addition, the symptoms must

- **cause clinically significant distress or impairment** in social, occupational, or other important areas of functioning
- **not be due to**
 - the direct physiological effects of a substance (e.g., a drug of abuse, a medication)
 - a general medical condition (e.g., hypothyroidism)
 - bereavement (after the loss of a loved one; however major depression may be present if symptoms persist for longer than 2 months, or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation)

*Derived from the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV TR)²⁴ The DSM-IV was originally published in 1994, and was updated in a text revision, DSM-IV TR, published in 2000. The next edition of the DSM, the DSM-V, is scheduled for publication in 2012.

Dysthymia

Dysthymia is a separate DSM-IV disorder with less severe but more long-lasting symptoms. Symptoms are not necessarily present every day, but must be continuously present for **2 years** (see Box 2). While major depression represents an acute or subacute change from a patient's baseline state, dysthymia represents a more chronic condition, with the baseline state itself characterized by a depressed mood.

Because dysthymia is a chronic condition it should be distinguished from **chronic major depressive disorder**, which occurs when a patient meets the criteria for major depression over an extended period of time (>2 years) without remission. Chronic major depressive disorder is more severe but less common; most patients with depressive symptoms for 2 or more years will meet criteria for dysthymia rather than chronic major depression.

Dysthymia (DSM-IV TR)*

Depressed mood

- A. for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 years
- B. presence, while depressed, of 2 or more of the following:
 - poor appetite or overeating
 - insomnia or hypersomnia
 - low energy or fatigue
 - low self-esteem
 - poor concentration or difficulty making decisions
 - feelings of hopelessness
- C. during the 2-year period of the disturbance, the person has never been without the symptoms in criteria A and B for more than 2 months at a time

In addition

- no major depressive episode has occurred during the first 2 years of the disturbance (i.e., the disturbance is not better accounted for by chronic major depressive disorder, or major depressive disorder in partial remission)
- the symptoms must not be due to the direct physiological effects of a substance or a general medical condition
- the symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

*Derived from the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV TR)²⁴

Minor depression

When a patient has some of the symptoms of depression or dysthymia but does not meet full criteria, **minor depression** or **subsyndromal depression** is a more appropriate diagnosis. This is not an official DSM-IV diagnosis but has often been used in research studies of depression treatments, particularly in trials of antidepressants.

For clinical purposes, minor depression can be thought of as similar to dysthymia in terms of symptom severity, although it is episodic rather than chronic. It is also similar to major depression in terms of being episodic, although it is generally not severe enough to impair functioning to the degree of major depression.

Minor or subsyndromal depression in the elderly is defined by the presence of at least 2 of the secondary symptoms of depression noted above, or screening positive on an instrument such as the General Health Questionnaire (see below), without meeting full criteria for major depression.

Minor Depression (not a DSM-IV diagnosis)

Either or both of the following during the same 2-week period

- depressed mood
- loss of interest or pleasure

Plus 2 or less of the following symptoms

- significant weight gain or loss (when not dieting), or change in appetite
- insomnia or hypersomnia
- psychomotor agitation or retardation
- fatigue or loss of energy
- feelings of worthlessness or excessive or inappropriate guilt
- diminished ability to think or concentrate, or indecisiveness
- recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

The table below summarizes major depression, minor depression, and dysthymia in terms of symptom severity and time course. As noted, major depression is by definition episodic and represents a substantial departure from the patient's usual baseline state,

Table 1: Time course and level of symptom severity for depressive syndromes

	Severe symptoms of depression	Moderate symptoms of depression
Episodic time course	Major depression	Minor depression
Chronic time course	Chronic major depression (uncommon)	Dysthymia

while minor depression has a similar time course but with less severe symptoms. When patients have chronic depressive symptoms, the diagnosis is much more likely to be dysthymia, although more severe chronic major depression must be considered.

BOTTOM LINE: Although major depression, minor depression, and dysthymia share many of the same diagnostic criteria, understanding the time course and severity of symptoms will help in making the correct diagnosis.

Depression screening and diagnosis

Depression often goes undetected in primary care, especially in older patients. Conversely, patients who report being sad (often for appropriate

situational reasons) or present with somatic complaints, are sometimes incorrectly labeled as “depressed,” and committed to a course of medication that is unlikely to help. To address this, simple, brief screening tools have been created for use in primary care. They can help identify patients likely to be suffering from depression, but by themselves are not sufficient to make a diagnosis or to institute treatment. **A positive screen should spur further questions to identify whether the patient meets more specific diagnostic criteria for one of the depressive disorders, as defined in Boxes 1-3.**

One useful scale developed specifically for use in the elderly is the **Geriatric Depression Scale** (GDS). A 15-question form of the GDS is widely used in research and has been validated as a diagnostic tool for depression in the elderly.²⁵ Because the 15-question tool may not be practical in many busy practices, a 5-item form (below) has been used as a screening tool in even the busiest practice. It has very good sensitivity and specificity, and significant agreement with the 15-item version (sensitivity=0.94 and specificity=0.81).²⁶

The Geriatric Depression Scale – 5 Item Version

1. Are you basically satisfied with your life? (depressed = “no”)
2. Do you often get bored? (depressed = “yes”)
3. Do you often feel helpless? (depressed = “yes”)
4. Do you prefer to stay at home rather than going out and doing new things? (depressed = “yes”)
5. Do you feel pretty worthless the way you are now? (depressed = “yes”)

Two or more depressive responses suggests the diagnosis of depression.²⁷

The 15-item version of the GDS may be useful in assessing treatment effect in a specific patient already diagnosed with depression, and in written form can be given to the patient to fill out while in the waiting room (for a copy, see Appendix 1).

Even a 5-question tool may be overly burdensome when managing older patients with multiple other medical problems. To address this concern, a screening tool with only 2 questions has been tested and evaluated, and found to have a sensitivity of 97% and a specificity of 67%.²⁸ **The 2 questions are:**

- "During the past month, have you been bothered by feeling down, depressed or hopeless?"
- "During the past month, have you been bothered by little interest or pleasure in doing things?"

While no screening tool is best for all clinicians, the use of any tool, when applied routinely to elderly patients, can substantially improve the identification and treatment of depressed patients.

BOTTOM LINE: By using a brief diagnostic screening tool, clinicians can effectively screen for depression in elderly patients.

Differential diagnosis

Several medical illnesses can cause symptoms of depression, such as unrecognized thyroid disease,²⁹ structural brain diseases such as stroke³⁰ or tumor,³¹ Parkinson's disease,³² metabolic conditions such as vitamin B12 deficiency,³³ infections such as HIV,³⁴ and certain cancers, such as pancreatic cancer.³⁵ For this reason, a thorough general medical history must be taken, and relevant laboratory or imaging studies be pursued.

Dementia poses a particular challenge in differential diagnosis since, in its early stages, dementia may present with some symptoms of depression. Cognitive impairment may lead patients to change their habits, perhaps abandoning hobbies and interests, thus presenting with apparent apathy or anhedonia. At the same time, depression itself can cause cognitive impairment in both young and elderly patients, especially with symptoms of worsening concentration and insomnia. Clinicians should assess and follow cognitive function, and if available, should consider neuropsychological testing. If clinically convincing symptoms of depression are present, it is reasonable to treat the depression, using the approaches described in the following sections. Some data suggests that antidepressants may be associated with an improvement in cognitive performance if depression has played a role in impaired cognition.³⁶ An extensive Cochrane review of the literature of antidepressant trials in dementia found evidence that they are probably helpful in this context.³⁷

Non-pharmacologic treatment options in major depression

Although antidepressant medications have become the most common form of treatment for depression, other treatment modalities still have an important role. This is particularly the case for elderly patients, who may be more at risk of medication side effects or of interactions between antidepressants and medications for other medical conditions. Referring patients for non-pharmacologic treatments will depend on resource availability in the community; but when such services are available, they can represent a useful treatment option for older patients with major depression.

Psychotherapy

Psychotherapy can be considered in patients with relatively intact cognitive status, and has the considerable advantage of not causing medication side effects. Although there is a widespread belief that antidepressants are more effective for all kinds of depression than talk therapy ("A pill is worth a thousand words"), this stereotype is not borne out in fact. One recent meta-analysis of studies that compared psychotherapy and medications in elderly patients found that they both worked about equally well.³⁸ In at least one study, depressed elderly reported a preference for psychotherapy over medication.³⁹

Negative attitudes by clinicians and many patients toward talk therapy has its roots in reactions towards older forms of psychotherapy, including psychoanalytic approaches based on the work of Freud and others. Such treatment often focused on early-life family issues, frequently went on for years, and has generally not withstood rigorous evaluation of its effectiveness. However, recent years have seen the development of more modern approaches to psychotherapy which have accumulated a far more impressive track record of efficacy. This section describes two types of psychotherapy whose outcomes have been documented in carefully conducted research trials in the elderly. Other forms of psychotherapy are also worthwhile considerations, such as supportive psychotherapy⁴⁰ and psychodynamic therapy,^{41, 42} which have demonstrated evidence for efficacy in younger adults and may be similarly effective in the elderly.

Cognitive-behavioral therapy (CBT) is a form of time-limited individual psychotherapy (usually 10-12 sessions) that seeks to help the patient modify the maladaptive cognitions, beliefs, assumptions and behaviors that maintain depressive symptoms. A recent Cochrane review meta-analysis of psychotherapy for adults 55 and over with major depression evaluated outcomes from 5 CBT trials and found that patients treated with CBT had significant improvements in depression symptoms compared to a control population of patients on a waitlist to begin treatment.⁴³ Another analysis in that study found no difference in effectiveness between CBT and psychodynamic psychotherapy in three treatment trials.⁴³

Interpersonal psychotherapy (IPT) is also time-limited and focused, but is based on a more psychodynamic or psychoanalytic approach. IPT focuses on goals relating to interpersonal relationships: role transitions, role conflicts, prolonged grief, and interpersonal deficits. Several studies have demonstrated that IPT is equally as effective as antidepressants in all-age adults,⁴⁴ and one study found it to be equal to nortriptyline in preventing relapse of depression in

adults 60 years and older.⁴⁵ Another study demonstrated that a series of 10 sessions of IPT was more effective than treatment-as-usual in a group of 143 elderly depressed patients.⁴⁶ IPT was the one type of psychotherapy chosen for the Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT), a large (n=598), multi-site, multi-modal treatment study of depression.⁴⁷

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is incorrectly viewed by many as an outmoded, somewhat barbaric treatment for psychiatric disease. This perception is based on an older version of that therapy, which has changed considerably in recent years. Current ECT includes anesthesia to prevent muscle movements and injury associated with tonic-clonic seizures. In fact, it may be the only effective treatment for an extremely withdrawn, severely depressed older patient whose illness is so severe that it prevents all oral intake. In that setting, ECT can literally be life-saving. It has been shown to have better short-term efficacy and faster onset of effect in older patients,⁴⁸ and is usually given in 6-12 sessions over a period of 2-5 weeks. Side effects include anterograde and retrograde amnesia, which is mostly transient, post-ictal confusion, and post-treatment muscle aches. Surprisingly, treated patients, including the elderly, score higher on intelligence tests shortly after ECT than in the untreated, depressed state.^{49, 50}

While there is a dearth of randomized, controlled trials of ECT in the elderly, its efficacy has been established in trials of all-age adults, and a meta-analysis demonstrated superiority over pharmacotherapy for severe depression.⁵¹ Some studies have suggested that ECT is more effective than medication in the elderly.⁵² In a review of naturalistic, prospective studies of ECT in the elderly, response rates (mostly defined as "complete recovery") ranged from 55% to 85%, with higher success rates in the oldest patients reported in some of those studies.⁵³

Referral to specialists who can administer ECT should be considered in severely depressed elderly patients, particularly when psychotic symptoms are present or when there is a significant reduction in food and fluid intake.⁴⁸ Older patients who are taking multiple medications for comorbid diseases are particularly vulnerable to antidepressant side effects,⁵³ making ECT a potentially attractive option in this population.

BOTTOM LINE: Non-pharmacologic treatment modalities, such as cognitive behavioral therapy, interpersonal psychotherapy, and ECT, are effective in the management of major depression, and may be preferred for some elderly patients.

Pharmacologic treatment options in major depression

While tricyclic antidepressants such as amitriptyline (Elavil) have been in use for many decades, it was the advent of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Prozac) in the late 1980s that brought antidepressants into the mainstream of clinical practice and the public consciousness. Coupled with vigorous promotion to clinicians and to patients, the introduction of these drugs created a widespread belief in their effectiveness that is often at odds with the research data. This section presents an overview of that evidence.

The first generation antidepressants included tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs); but because of their side effect profiles, these medications are rarely used by generalists to treat depression in the elderly. Although older patients previously treated with TCAs may remain on these agents, and although TCAs are sometimes used in low doses for conditions other than depression, their side effect profiles in the elderly have made them less desirable as first-line agents. MAOIs can cause hypotension, peripheral edema, neurological effects (headache, insomnia, myoclonus), and a well-documented risk of hypertensive crisis caused by interactions with products such as tyramine-containing foods (such as certain cheeses and red wine) and sympathomimetic medications (such as pseudoephedrine). As a result, they are usually avoided altogether in elderly patients.

Table 2: Major classes of antidepressants and their mechanisms of action

Drug Class	Mechanism of action	Examples (Brand name)
Selective serotonin reuptake inhibitors (SSRIs)	Selectively inhibit the reuptake of serotonin (5-HT) at the presynaptic neuronal membrane	citalopram (Celexa) sertraline (Zoloft) paroxetine (Paxil) escitalopram (Lexapro) fluoxetine (Prozac)
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Inhibit reuptake of both serotonin and norepinephrine; weakly inhibit dopamine reuptake	venlafaxine (Effexor) duloxetine (Cymbalta)
Monoamine oxidase inhibitors (MAOIs)	Competitively inhibit monoamine oxidase; agents in the class differ in their reversibility and their activity against MAOa and MAOb	phenelzine (Nardil) tranylcypromine (Parnate)
Serotonin modulators	Selective inhibitor of serotonin reuptake; also acts as a 5HT ₂ antagonist	trazodone (Desyrel)
Dopamine-norepinephrine reuptake inhibitors	Inhibit dopamine reuptake with some effect on norepinephrine	bupropion (Wellbutrin)
Noradrenergic and specific serotonergic antidepressant	Block presynaptic central alpha ₂ -adrenergic autoreceptors, resulting in increased neurotransmission of noradrenaline and serotonin; also block post-synaptic 5HT ₂ and 5HT ₃ receptors	mirtazapine (Remeron)
Tricyclic antidepressants (TCAs)	Inhibit reuptake of norepinephrine and serotonin into presynaptic terminals	amitriptyline (Elavil) imipramine (Tofranil) nortriptyline (Pamelor) desipramine (Norpramin)

Newer antidepressants, in particular the selective serotonin reuptake inhibitors (SSRIs), have about the same efficacy as the TCAs, but a side effect profile that is different and somewhat more benign. They are also considerably safer in case of overdose. As a result, the SSRIs are generally considered first line drug therapy for depression in expert guidelines.⁵⁴ Other agents include serotonin-norepinephrine reuptake inhibitor (SNRIs), such as venlafaxine and duloxetine, dopamine-norepinephrine reuptake inhibitors such as bupropion, and serotonin modulators such as trazodone.

This section reviews the efficacy, safety, and cost of these commonly used second-generation antidepressants in the elderly. Because elderly patients previously treated with TCAs may remain on these agents, data on TCAs will be reviewed as well. **MAOIs are rarely used in the elderly, and when used are prescribed by specialists. Trazodone is generally a second or third-line agent for the treatment of depression in the elderly.** Thus, these two drug classes will not be discussed below; patients taking these medications should have a specialist involved in their care.

Efficacy of antidepressant medications

Determining the efficacy and safety of antidepressants is difficult, because many of the studies evaluating antidepressants have:

- included a small number of patients
- been of short duration
- diagnosed depression in a variety of ways
- included patients with different severities of illness
- used different outcome measures
- largely been funded by the pharmaceutical industry⁵⁵

Nevertheless, there are some high quality studies and systematic reviews which provide useful information to help guide drug choices. We summarize this information below.

How effectively do antidepressants reduce depressant symptoms?

In contrast to drug classes that seek to lower blood pressure or LDL cholesterol, **there is no single universally accepted way to define the response to antidepressant therapy.** In addition, it is harder in depression compared to these non-psychiatric conditions to precisely define the severity of illness at study entry. Many trials that have evaluated antidepressant efficacy have relied on scales (such as the Hamilton Depression Rating Scale [HAM-D])⁵⁶ and define response as achieving a certain score change or getting the score to fall below a given threshold.⁴³

Trials have either compared specific antidepressant agents to placebo (a minimum standard, which allows for an estimate of the absolute magnitude of benefit of these therapies) or to each other (which provides an assessment of the relative benefits of different agents).

Placebo-controlled trials

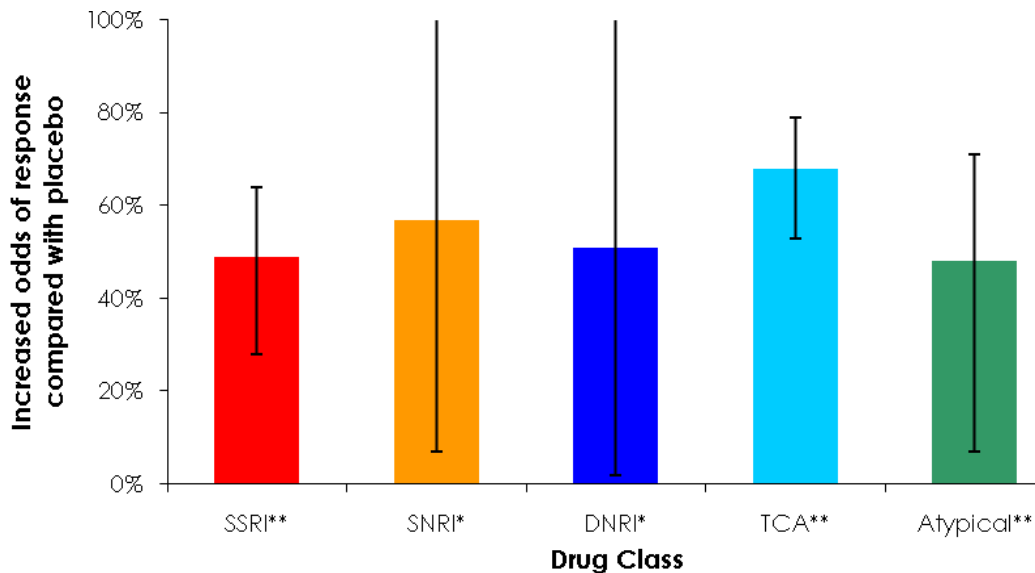
Most antidepressants used today have been demonstrated to be better than placebo for the treatment of the symptoms of depression, a minimalist criterion which is usually adequate to obtain approval for marketing from the Food and Drug Administration (FDA). The SSRIs have been the most widely studied.⁵⁵

Two recent meta-analyses focusing on elderly patients synthesized these placebo-controlled trials.^{43, 55} In the most recent of these,⁵⁵ an average of 44% of patients receiving drug therapy had significant improvement in their depression symptoms (i.e., $\geq 50\%$ improvement in the HAM-D score), compared to a slightly lower 36% of patients receiving placebo. In relative terms, antidepressants

increase by 40% the odds that a patient's symptoms will be significantly reduced (see Figure 2). Note that 40% represents increase in the odds of improvement, not the level of improvement itself. The magnitude of response from antidepressant therapy depends on the patient's baseline depression severity, with patients who are severely depressed far more likely to benefit from medication than those with milder depression. Put another way, placebo works about as well as antidepressants for patients with mild depression, but not for patients with severe depression.⁵⁷

Figure 2: In patients with major depression, the increased likelihood of responding to therapy compared to placebo is about the same for different antidepressant classes.

The top of each colored bar represents the increased odds of responding for that class of agents compared to placebo. The thin error bars represent the 95% confidence intervals for the odds of responding. Atypical antidepressants include mirtazapine, minaprine and medifoxamine, the last two of which are not approved for use in the U.S. The data presented are from Nelson et al.⁵⁵ and Wilson et al.⁵⁸



* Data from Nelson JC, Delucchi K, Schneider LS. Efficacy of Second Generation Antidepressants in Late-Life Depression: A Meta-Analysis of the Evidence. *Am J Geriatr Psych.* May 12 2008.

** Data from Wilson K, Mottram P, Sivanranthan A, Nightingale A. Antidepressant versus placebo for depressed elderly. *Cochrane Database Syst Rev.* 2001(2):CD000561

Although the improvements relative to placebo appear to be slightly larger for some agents than for others, these studies did not compare agents “head-to-head,” and the confidence intervals for each substantially overlap, indicating that there are probably no significant differences in efficacy between classes. Further, these small relative differences in the odds of improving translate to very small absolute differences in outcomes. While these studies focused primarily on efficacy, in clinical practice, side effect profiles and costs are also important considerations, especially since many depressed patients treated with placebo also improve over time.

One of the largest studies to date was an 8-week trial in which 752 outpatients 60 years of age and older with a DSM-IV diagnosis of major depression and a HAM-D score of ≥ 18 were randomized to sertraline (50 mg daily for 4 weeks, which could be increased to 100 mg daily at the investigator's discretion), or placebo.⁵⁹ At the end of the study, 35% of patients randomized to sertraline as compared to 26% of patients receiving placebo had a 50% or greater reduction in their HAM-D score ($p=0.007$).

St. John's wort (hypericin) is a popular over-the-counter treatment for depression. However, rigorous clinical studies have not found it to be effective. One meta-analysis found aggregate evidence of effectiveness in 23 studies encompassing 1,757 outpatients,⁶⁰ but many of the studies had important methodological flaws. A better-conducted randomized controlled trial, published in 2001, compared hypericin to placebo (200 patients, average age 42.4 years)⁶¹ and found no difference in treatment of major depressive disorder.

BOTTOM LINE: Numerous prescription antidepressants are effective when compared to placebo for major depression. Meta-analyses suggest that most are similarly effective.

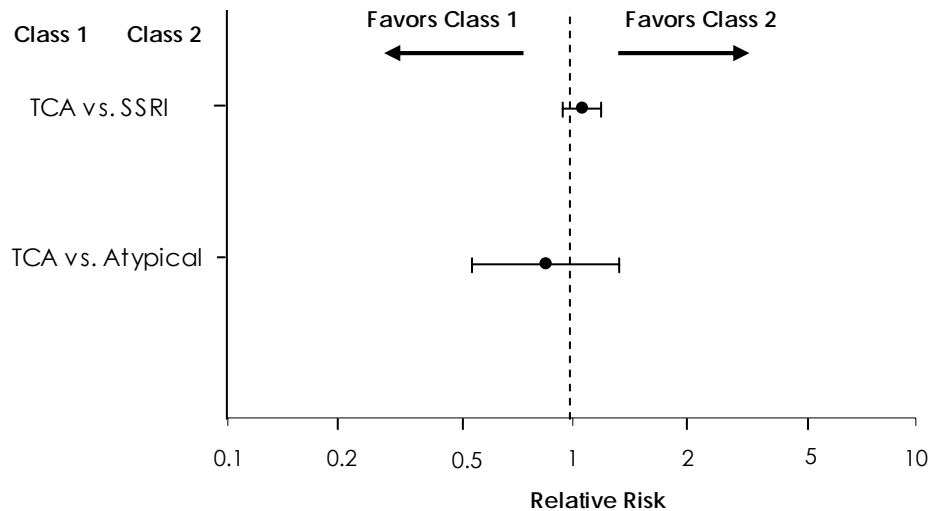
Head-to-head trials

Many small, generally short-term head-to-head trials compared the efficacy of different antidepressants, although only a small number of these were conducted in the elderly. The studies that do exist suggest that all of the available agents are equally effective.

A recent meta-analysis by the Cochrane collaborative summarized the comparative effectiveness of different classes of antidepressants specifically in the elderly.⁶² We summarize the results of this analysis below (Figure 3).

A larger meta-analysis evaluated the effects of second generation antidepressants (i.e., not TCAs and MAOIs) in depressed adults (i.e., not just the elderly). This comprehensive study included 55 head-to-head randomized controlled trials, and found very similar results to the Cochrane review presented above.⁶³ **Both of these meta-analyses suggest that on average, 50-70% of patients treated with antidepressants will respond to treatment.**

Figure 3: Comparative efficacy of different antidepressant classes. The figures represent the odds of failing to recover (generally defined as a 50% reduction in a patient's Hamilton-D score) with the 95% confidence interval. Atypical antidepressants include buspirone, bupropion, milnacipran, venlafaxine and reboxetine. The data presented are from Mottram et al.⁶²



We present more detailed evidence regarding specific drug class comparisons in the elderly below. (MAOIs, which are generally not recommended in the elderly, are excluded from this comparison.)

TCAs vs. SSRIs

Numerous randomized controlled trials have compared outcomes for depressed elderly patients using TCAs and SSRIs, all of which found equivalent efficacy for these classes of antidepressants. The specific agents evaluated have been:

- fluoxetine v. amitriptyline⁶⁴
- fluoxetine v. doxepin⁶⁵
- paroxetine v. doxepin⁶⁶
- paroxetine v. amitriptyline⁶⁷⁻⁶⁹
- paroxetine v. clomipramine^{70, 71}
- paroxetine v. nortriptyline^{72, 73}
- paroxetine v. imipramine⁷⁴
- citalopram v. amitriptyline^{75, 76}
- citalopram v. nortriptyline⁷⁷
- sertraline v. amitriptyline⁷⁸

TCAs vs. SNRIs

Two blinded studies in elderly patients compared venlafaxine with TCAs nortriptyline⁷⁹ and clomipramine.⁸⁰ The venlafaxine/nortriptyline study of 68 elderly patients with severe major depression indicated that the remission rate for both was similar (70% vs. 71%). The venlafaxine/clomipramine study (which also included a trazodone arm) involved 6 weeks of treatment in 170 patients, and also showed similar effectiveness and rates of side effects. No head-to-head trials in the elderly have compared TCAs with duloxetine.

TCAs vs. others

One study compared amitriptyline to mirtazapine in a total of 115 elderly patients over 6 weeks and found that both drugs improved scores on depression scales equally.⁸¹ Another study compared imipramine with trazodone in 60 depressed elderly outpatients and found similar efficacy between these agents.⁸² Similar results were obtained in a study comparing trazodone with amitriptyline in 106 elderly depressed inpatients.⁸³

SSRIs vs. SNRIs

Several SSRIs have been tested in head-to-head studies with venlafaxine in the elderly. Paroxetine has been tested in two studies – an 8-week single-blind study of elderly patients with resistant depression who did not respond to at least two previous trials of antidepressants⁸⁴, and a short, 4-week treatment of elderly inpatients in Taiwan.⁸⁵ In the trial of resistant depression patients, remission rates were higher for venlafaxine (60% vs. 30%). The trial of inpatients reported similar response rates (75% vs. 76%) and no differences in the mild observed adverse effects. Two additional studies comparing venlafaxine and paroxetine in all adults have found no significant differences between these agents.⁶³

Fluoxetine was compared to venlafaxine in a blinded trial of 300 elderly patients over 8 weeks. Both groups showed similar effectiveness in treatment of depression in terms of mean reduction in depression index scores.⁸⁶ However, a meta-analysis of studies comparing fluoxetine and venlafaxine in adult outpatients suggests that the response rate from venlafaxine may be slightly higher than from fluoxetine (relative risk 1.13, 95% confidence intervals 1.03-1.24).⁸⁷ Unfortunately, most of the studies were only of fair methodological quality, and it is unclear whether these results apply to elderly patients.

Citalopram was compared to venlafaxine in a study of 151 elderly patients with major depression. It found that the rate of full remission in elderly

patients with major depression was similar to the rate observed in younger adults (about 20% in both groups).⁸⁸

Sertraline was compared to venlafaxine in an elderly nursing home population with a mean age of 82 (this was the oldest average age in all the studies in this category), and this study again found equal efficacy between the agents tested.⁸⁹ Two studies in adult patients have confirmed these findings.⁸⁷

Studies comparing SSRIs (fluoxetine and paroxetine) with duloxetine in adults with major depression found no significant differences between these drugs.⁸⁷

BOTTOM LINE: SSRIs and SNRIs appear similar in terms of efficacy. Minor differences observed in studies of venlafaxine and fluoxetine have not been observed in the elderly.

SSRIs vs. Others

One study compared efficacy of fluoxetine and trazodone in 27 elderly depressed patients, but only 13 completed the 6-week study period.⁹⁰ Both agents were effective according to endpoint analyses. Several studies have compared different SSRIs (i.e., fluoxetine, paroxetine and sertraline) with nefazodone (a serotonin modulator like tradozone) in all adults and found equal efficacy between agents.⁸⁷

Another study compared the efficacy and safety of paroxetine and bupropion sustained release (SR) in the treatment of major depression in 100 elderly outpatients for 6 weeks.⁹¹ Measurements of efficacy were similar between the 2 treatment groups. A meta-analysis comparing SSRIs to bupropion in adult outpatients that included 5 randomized controlled trials also found no significant differences between the agents.⁹²

Mirtazapine and paroxetine have been compared in one study of elderly depressed patients.⁹³ Although the proportion of patients who achieved a response (i.e., a 50% reduction in HAM-D score) was slightly higher in the mirtazapine group (56% v. 50%), the difference was not statistically significant. Other studies in non-elderly adults also have not found any meaningful differences between mirtazapine and other SSRIs.^{94, 95}

SNRIs vs. Others

Venlafaxine has been studied in a head-to-head manner against both trazodone and bupropion and no differences in effectiveness have been found.⁸⁰

BOTTOM LINE: In head-to-head trials, the major classes of antidepressants are generally equally effective for the treatment of depression.

Comparisons within selected classes

An important question for clinicians is whether drugs from a class can be used interchangeably. There is a limited body of evidence (summarized below) that speaks directly to this question, but indirect comparisons do allow for the development of treatment recommendations.

*TCA*s

A single study has compared outcomes among TCAs exclusively in elderly patients. In that study, a 6-week blinded trial of trimipramine vs. doxepin in 37 “young elderly” patients, both drugs were equally effective in relieving symptoms of depression.⁹⁶ Indirect comparisons (i.e., comparisons of individual agents to placebo) suggest that all members of this class of drugs are equally effective.⁵⁸

*SSRI*s

Several studies have compared different SSRIs to each other for the treatment of depression in the elderly. A large group of studies conducted in non-elderly adults has demonstrated that most SSRIs are equally efficacious for the treatment of depression. Some trial data do suggest that small differences between individual SSRIs might exist; these are described in more detail below.

(a) Citalopram v. escitalopram

While no studies in the elderly have compared these two agents, they have been compared in 4 relatively large studies involving non-elderly depressed patients all of which compared appropriate doses of medications (escitalopram 10-20 mg v. citalopram 20-40 mg).⁸⁷ All 4 studies reported response rates for patients receiving escitalopram to be approximately 5-14% higher than patients receiving citalopram. A meta-analysis of these 4 studies shows that the odds of response (defined as a 50% improvement in the Montgomery Asberg Depression Rating Scale [MADRS]) as 19% higher for

patients receiving escitalopram (95% confidence interval 8-30%).⁹⁷ However, the magnitude of this effect as measured by the MADRS scale was only 1.25 points better for patients receiving escitalopram; it is unclear if this difference is clinically meaningful.⁹⁷

Of note, both of these drugs are produced by the same manufacturer, who funded all 4 of these studies. Citalopram is available as a generic drug; escitalopram, introduced around the time that the patent on citalopram was expiring, is its L-isomer and is identical in all other chemical respects, and is not available generically. There has been some controversy as to whether the doses of the two drugs used in this trial were perfectly comparable. No studies have compared these drugs in the elderly. Further, just as for citalopram, escitalopram has not been shown to be superior to the other antidepressants (i.e., venlafaxine, sertraline, paroxetine) against which it has been compared.⁹⁸⁻¹⁰¹

(b) Fluoxetine v. sertraline

A study involving 246 elderly subjects compared fluoxetine and sertraline over a 12-week period and showed no significant differences in response (71% for fluoxetine and 73% for sertraline).¹⁰² Several other studies in non-elderly adults have also found no significant differences between these drugs but a meta-analysis found that patients treated with sertraline had a 10% higher likelihood of responding to therapy, with borderline statistical significance (95% confidence interval 1-22%).⁹⁷

(c) Paroxetine v. fluoxetine

Several studies have compared fluoxetine and paroxetine. In one study of 106 elderly outpatients with depression over a 6-week time period, a significantly higher proportion of subjects responded to paroxetine than to fluoxetine.¹⁰³ Both treatments produced improvements in all measures of cognitive and behavioral function, but the effect of paroxetine was demonstrated earlier (in week 3). A meta-analysis that included this study and 5 others involving non-elderly adults found a non-significant increased likelihood of response from paroxetine compared to fluoxetine (relative risk 1.09; 95% confidence intervals 0.97-1.21).⁹⁷

This analysis did not include the largest study comparing these two agents, which was actually conducted in elderly outpatients.¹⁰⁴ The study enrolled 242 patients and those randomized to paroxetine had a faster response, but after 1 year, 60% of patients in both arms had a HAM-D score of <10.

(d) Immediate v. extended release formulations

Paroxetine in immediate and extended release formulations has been compared in elderly depressed patients.¹⁰⁵ This 12-week study showed equivalent reductions in HAM-D scores and the proportion of patients who achieved remission in both trial arms.

There are no published studies comparing daily and weekly fluoxetine as initial therapy for elderly patients with depression. These two regimens have been compared and found to be equivalent when used as continuation treatment for non-elderly adults who responded to acute treatment with fluoxetine 20 mg daily.¹⁰⁶ Of note, peak concentrations from once weekly fluoxetine are approximately the same as those from daily 20 mg dosing,¹⁰⁷ which is higher than the typical starting dose in the elderly patients.

BOTTOM LINE: Although direct data are limited, the available evidence suggests similar efficacy for antidepressants in the same drug class in the elderly. Some data from non-elderly patients suggests a potential advantage of escitalopram over citalopram, but the magnitude of this effect is relatively small.

Side effects of antidepressant medications

While the efficacy profiles of available drugs are strikingly similar, antidepressants differ substantially in their side effect profiles. Some side effects are common among all members of a therapeutic class, while others are drug-specific. TCAs have a narrow therapeutic index and in overdose can have fatality rates substantially higher than for other classes of antidepressants.¹⁰⁸ "Second generation" antidepressants have different side effects, and are generally safe if excessive amounts are taken. The typical side effects of these medications and TCAs are summarized in Table 3 below.

Abrupt cessation of SSRIs, SNRIs and TCAs can lead to a "discontinuation syndrome" that has both somatic and psychiatric components. The symptoms typically occur within days of discontinuation and may include dizziness, nausea, fatigue, muscle aches, chills, anxiety, and irritability.¹⁰⁹ Although these symptoms are not life-threatening and usually dissipate over one to two weeks, they can be very uncomfortable. Symptoms are more common and pronounced when discontinuing SSRIs with short half-lives and those without active metabolites.¹¹⁰ Paroxetine is the SSRI most commonly associated with discontinuation syndrome, and similar symptoms have been noted with venlafaxine.^{111, 112} In contrast, fluoxetine may not have any discontinuation side effects. As a result, when SSRIs, SNRIs and TCAs are discontinued, a slow tapering

over several weeks is recommended, except for fluoxetine, whose long half-life, problematic in other respects, causes it to “self-taper.”

Table 3: Side effects and drug-drug interactions for commonly used antidepressants

Drug class	Typical side effects/warnings	Comments	Drug-drug interactions
Selective serotonin reuptake inhibitors (SSRIs)	gastrointestinal symptoms (usually dose-related, mild and transient), insomnia, agitation, headache, sexual dysfunction; withdrawal side effects vary by drug; fairly safe in overdose	<i>fluoxetine</i> : longest half-life, side effects can persist for weeks after it is discontinued ¹¹³ <i>paroxetine</i> : short half-life increases risk of discontinuation side effects <i>citalopram</i> : conflicting evidence whether citalopram is more toxic in overdose than other SSRIs	All SSRIs inhibit the cytochrome P450 system, which can increase serum concentrations of drugs metabolized by this system, including most other antidepressants, analgesics and many cardiovascular drugs. Fluoxetine has a particularly high potential for drug interactions.
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	nausea, diarrhea, insomnia, agitation, headache, dry mouth, constipation, sexual dysfunction associated with withdrawal effects; higher risk of toxicity in overdose than SSRIs ¹¹⁴	<i>venlafaxine</i> : associated with hypertension, especially in doses ≥ 200 mg daily <i>duloxetine</i> : contraindicated in patients with uncontrolled narrow angle glaucoma; should not be used in patients with hepatic insufficiency	Unlike the SSRIs, they have little effect on the cytochrome P450 system ¹¹⁵ but are metabolized by it. Thus, significant potential for drug interactions exist.
Bupropion	headache, insomnia, agitation, weight loss	contraindicated for patients with seizure disorder	Limited data has been collected. Because bupropion is extensively metabolized by the liver, some drugs (e.g., cyclophosphamide) may increase bupropion levels. Bupropion also mildly inhibits CYP2D6
Mirtazapine	dry mouth, sedation, peripheral edema, constipation, appetite stimulation leading to weight gain; ¹¹⁶ more risky in overdose than SSRIs but limited information; withdrawal side effects are possible		Mirtazapine is metabolized by cytochrome p450 system (thus levels are increased by drugs such as ketoconazole). It also is a weak inhibitor of some CYPs.
Tricyclic antidepressants (TCAs)	anticholinergic effects (dry mouth, sweating, urinary retention, blurred vision, confusion), orthostatic hypotension, constipation, conduction abnormalities, sedation; withdrawal side effects if stopped abruptly; significantly higher fatality risk in overdose than other antidepressants	“secondary amine” subclass (nortriptyline and desipramine) appear to have fewer side effects although desipramine has a particularly higher fatality risk in overdose	TCAs are metabolized by the cytochrome P450 system, so co-prescription of P450 inhibitors such as certain antibiotics can raise TCA levels and increase risk of side effects. They have additive effects with other agents that prolong QT interval.

Hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is one uncommon but important potential side effect of SSRIs. One prospective study of the effect of paroxetine in elderly patients found a 12% risk of developing hyponatremia, defined as sodium less than 135, over a 12-week period.¹¹⁷ Evaluations of spontaneous reports of adverse effects after SSRI use suggest that hyponatremia may be a complication of numerous SSRIs.¹¹⁸ While the precise incidence is not well known, clinicians need to be aware of the possibility of hyponatremia after SSRI use, especially in the elderly.

Serotonin syndrome is a potentially life-threatening but rare condition associated with massive overdoses of serotonergic medications such as SSRIs or combinations of SSRIs and other serotonergic medication. The condition is due to increased serotonergic activity in the central nervous system. Clinical manifestations include mental status changes (anxiety, agitated delirium, disorientation), autonomic manifestations (diaphoresis, tachycardia, hyperthermia) and neuromuscular hyperactivity.

Other rare, but potentially serious, side effects of antidepressants include bleeding and bone loss.¹¹⁹ SSRIs appear to double a patient's risk of bleeding¹²⁰ although the absolute risk remains quite low, especially for patients who do not have any other risk factors. SSRIs may also increase the risk of bone loss. Two recent studies suggest that rate of bone mineral density (BMD) loss were higher in patients taking SSRIs rather than placebo.^{121, 122} No increased rate of bone loss was observed with TCAs.¹²¹ Although this increase in BMD loss may be sufficient to lead to higher rates of fragility fractures,¹²³ the relationship between SSRIs and osteoporosis needs to be better studied.

In recent years, antidepressant use has been linked to higher rates of suicidal ideation (but not completed suicide) in adolescents and young adults using these agents. As a consequence, "black-box" warnings have been added to the labels of these medications.¹¹⁹ Although the risk of suicidality in older adults with depression is particularly high, antidepressants themselves appear to reduce, not increase, the risk of suicide among patients 65 years and older.¹²⁴

Rates of specific side effects

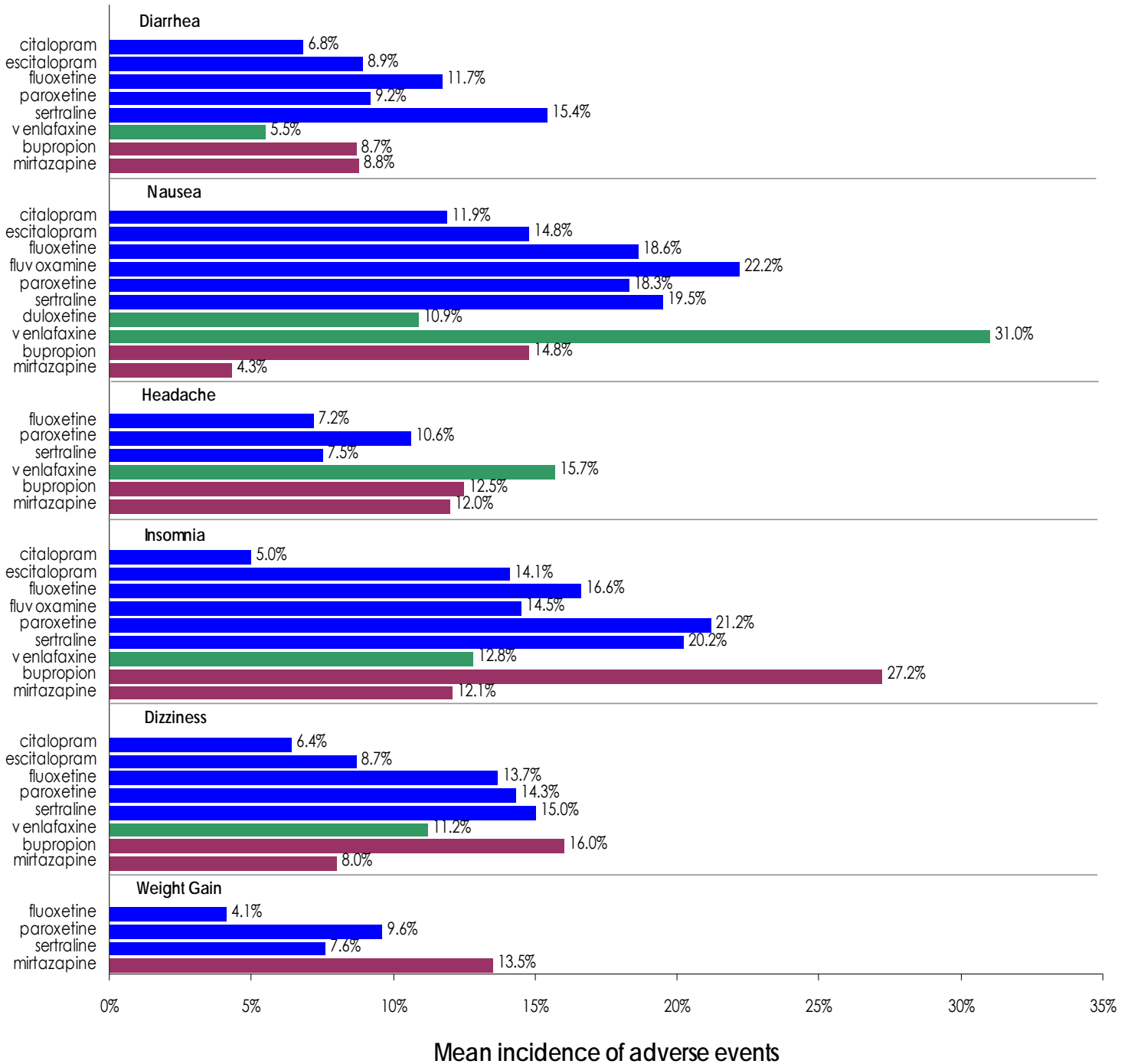
Rates of specific side effects from commonly used second generation antidepressants as observed in clinical trials of non-elderly adults are summarized in Figure 4. Some differences are apparent from this analysis:

- Most antidepressants are associated with side effects.
- Among the SSRIs, citalopram appears to have the lowest risk of side effects.

Figure 4: Side effects commonly observed for second-generation antidepressants.

Data is derived from studies of non-elderly adults synthesized by Gartlehner et al. ⁹⁷

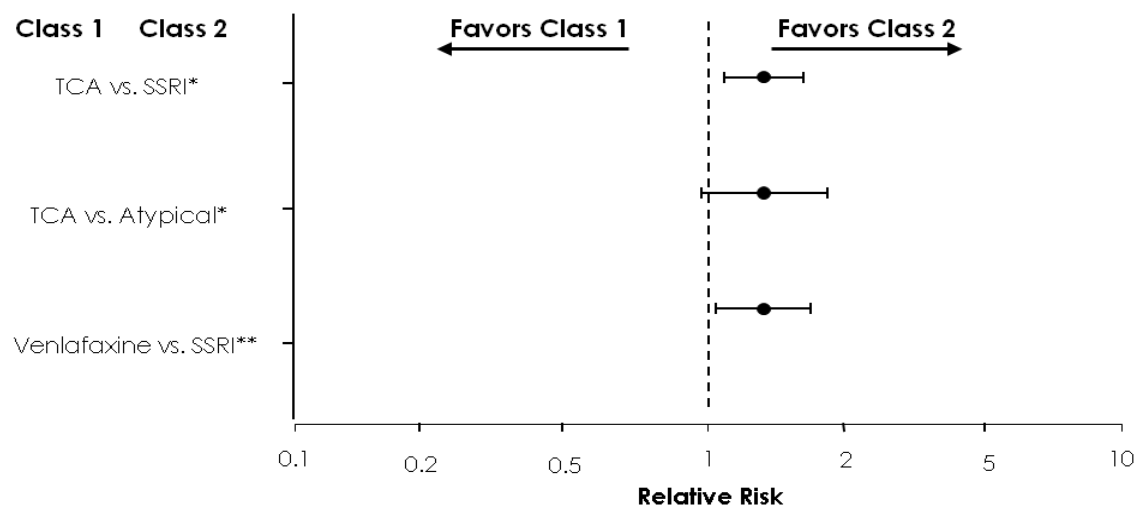
Blue = SSRI, green = SNRI, purple = other



Discontinuation rates

Most studies have not used standardized instruments to quantify adverse reactions,⁶² making these studies an unreliable source to assess side effects. An alternative approach is to evaluate the pattern of patients discontinuing their trial drug because of side effects (regardless of the particular side effect that is prompting withdrawal). This information is summarized in Figure 5.

Figure 5: Comparative tolerability of different antidepressant classes. The figure represents the odds of drug discontinuation due to side effects with 95% confidence intervals. Atypical antidepressants include buspirone, bupropion, milnacipran, venlafaxine and reboxetine. Data was obtained from Mottram et al.⁶² and Gartlehner et al.⁹⁷



* Data from Mottram P, Wilson K, Strobl J. Antidepressants for depressed elderly. *Cochrane Database Syst Rev.* 2006(1):CD003491

** Data from Gartlehner G, Hansen R, Kahwati L. *Drug Class Review on Second Generation Antidepressants.* 2006.

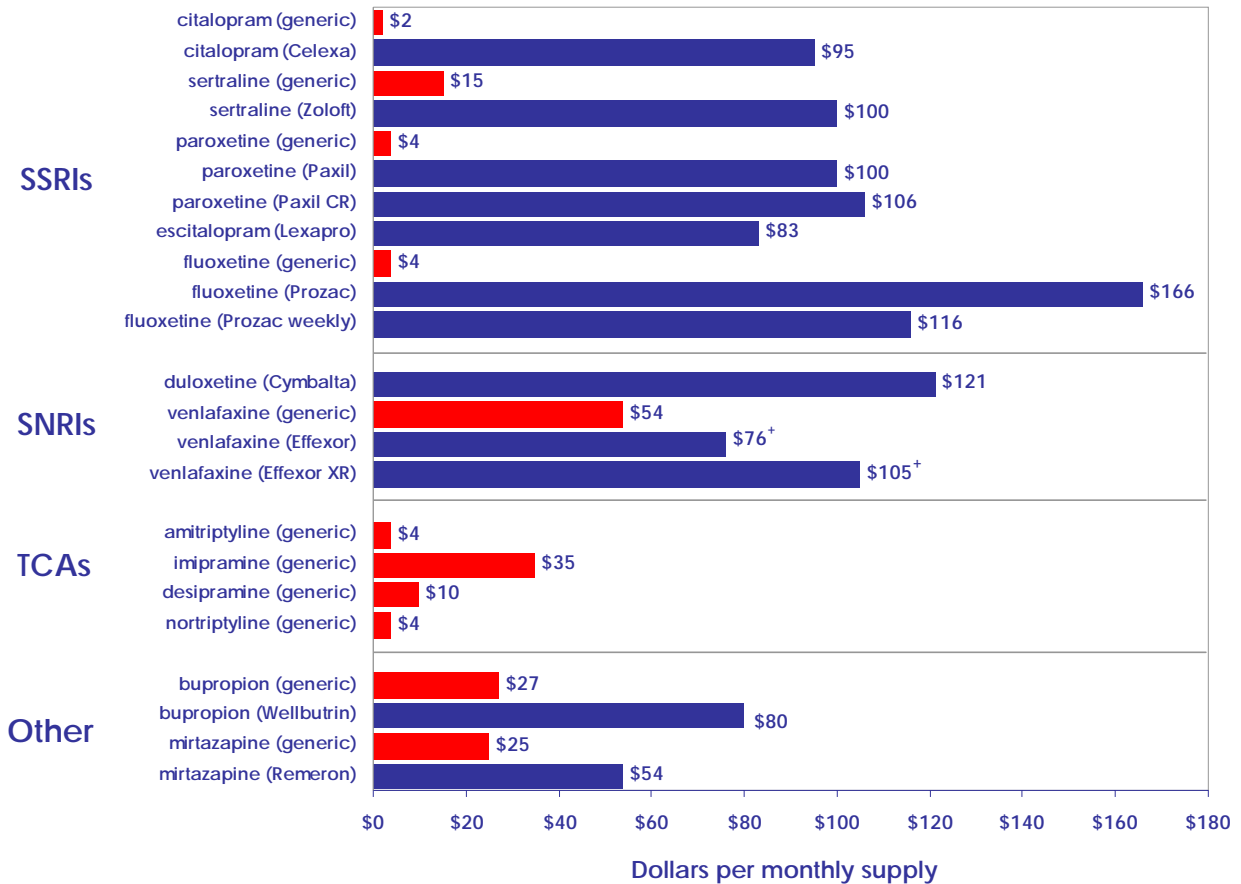
Based on this analysis, rates of discontinuing TCAs and venlafaxine are higher than those observed for SSRIs in the elderly. Discontinuation rates for other second-generation antidepressants among non-elderly patients also appear not to be significantly different from each other.⁹⁷

BOTTOM LINE: Each class of antidepressants is associated with its own side effect profile. TCAs have higher side effect risks and should be avoided in the elderly. Some individual SSRIs are also problematic for older patients.

Cost of antidepressant medications

Cost may be an important determinant in medication choice, especially when considering the relatively similar efficacy of most major antidepressants. This is an especially important consideration for patients exposed to potentially high co-payments for their drug regimens.

Figure 6: Monthly costs of antidepressants.*



*Monthly price is for lowest recommended starting doses in the elderly. Figure includes the lowest prices obtained 5/9/08 from drugstore.com and walmart.com. Many generics are available for \$4/30-day supply or \$10/90-day supply.

+ Venlafaxine lost patent protection in June 2008. Prices for Effexor and Effexor XR are expected to drop substantially over the next year.

There are generic versions of antidepressants in every antidepressant class that provide the most cost-effective strategy for treatment. Some antidepressants are available in an extended-release form that reduces the frequency of administration, which may increase medication adherence. Examples of these are venlafaxine and bupropion. However, there is surprisingly little evidence documenting improved compliance with such extended-release formulations. Paroxetine is also available in a controlled release form (Paxil CR) that, as noted in an earlier section, provides minimal improvement over regular paroxetine, which already has once-daily dosing. Fluoxetine is available as a weekly formulation but is only used for patients who have responded to daily fluoxetine.

BOTTOM LINE: There is a wide range in the cost of available antidepressants. A number of highly effective medications are available as generics which are substantially less expensive than brand name medications.

Putting it all together: recommendations for initiating treatment

Table 4 summarizes the comparative efficacy, safety, and cost of commonly used antidepressants. Green boxes indicate the best outcome, yellow boxes indicate intermediate outcomes, and red boxes indicate an important problem.

Table 4: Summary of comparative efficacy, safety and cost of antidepressants

Class	Drug	Efficacy	Safety								Cost*	Overall
			Anticholinergic effects	Drowsiness	Insomnia and agitation	GI	Headache	Withdrawal effects	Drug-drug interactions	Risk in overdose		
SSRI	citalopram (Celexa)	Green	Green	Green	Yellow	N	Yellow	Yellow	Yellow	Yellow	Green	Green
	sertraline (Zoloft)	Green	Green	Green	Yellow	N	Yellow	Yellow	Yellow	Green	Green	Green
	paroxetine (Paxil)	Green	Green	Green	Yellow	N	Yellow	Red	Yellow	Green	Red	Yellow
	escitalopram (Lexapro)	Green	Green	Green	Yellow	N	Yellow	Yellow	Yellow	Green	Red	Yellow
	fluoxetine (Prozac)	Green	Green	Green	Yellow	N	Yellow	Green	Red	Green	Green	Yellow
SNRI	venlafaxine (Effexor)	Green	+	Green	Yellow	N	Yellow	Red	Yellow	Yellow	Ψ	Red
	duloxetine (Cymbalta)	Green	Green	Green	Yellow	N	Green	Red	Yellow	Yellow	Green	Yellow
TCA	amitriptyline (Elavil)	Green	Red	Red	Green	C	Green	Red	Yellow	Red	Green	Red
	imipramine (Tofranil)	Green	Red	Red	Green	C	Yellow	Red	Yellow	Red	Yellow	Red
	nortriptyline (Pamelor)	Green	++	Red	Green	C	Green	Red	Yellow	Red	Green	Red
	desipramine (Norpramin)	Green	++	Red	Green	C	Green	Red	Yellow	Red	Green	Red
Other	bupropion (Wellbutrin)	Green	Green	Green	Red	Yellow	Yellow	Green	Yellow	Yellow	Yellow	Yellow
	mirtazapine (Remeron)	Green	+	Red	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow

Green = best outcome; yellow = intermediate outcome; red = problem

N = nausea/vomiting; C = constipation

* Based on generic formulation

+ Anticholinergic-like side effects, likely attributable to adrenergic activation

++ These agents may have less anticholinergic effects than other TCAs but they are still associated with a high degree of side effects in the elderly.

Ψ Venlafaxine lost patent protection in June 2008. Prices for Effexor and Effexor XR are expected to drop substantially over the next year.

An antidepressant should be chosen based on clinical efficacy, side effects, potential drug interactions with existing medications, and cost. Although the efficacy of antidepressant classes is roughly equivalent, the TCAs have higher rates of adverse events and drug-drug interactions, and should not be first-line treatments in the elderly. Patients who are already taking these medications chronically may be able to continue taking them, but new starts should be avoided.

With the above considerations in mind, citalopram (10-20 mg/day) or sertraline (25-50 mg/day) are recommended as initial treatment in most depressed elderly patients. These two agents offer good clinical efficacy, and the relatively favorable side effect profile and low cost of these medications

help to promote patient adherence to the prescribed regimen. Citalopram was the drug chosen for evaluation as starting therapy in the federally-funded STAR-D study of depressed patients, described in greater detail below. While escitalopram may offer a modest incremental benefit in a small subset of patients, citalopram offers almost identical efficacy at a fraction of the cost.

Prior to initiating therapy, an initial evaluation should always include an assessment of whether the patient has indications for urgent or emergent psychiatric referral, including:

- suicidality or the intent to harm others (patients with such risks should be treated immediately in an emergency setting);
- whether the depression has severe features such as psychosis, minimal verbal interaction, or severely restricted food intake (a specialist should be contacted and ECT should be considered);
- whether the patient has any manic symptoms, because treatment options for patients with bipolar disorder are substantially different from those with unipolar depression

Of course, treatment must be individualized. For example, in elderly patients with marked insomnia or weight loss, mirtazapine may be particularly useful. In contrast, bupropion may be considered in patients who have fatigue or poor concentration, because of its stimulating properties. When complicated comorbid symptoms are present, early specialist consultation can help guide the choice of antidepressant.

Table 5: Starting doses and administration of antidepressants in the elderly

Drug Class	Examples (brand name)	Starting doses in the elderly	Time of administration
Selective serotonin reuptake inhibitors (SSRIs)	citalopram (Celexa)	10-20 mg	morning
	sertraline (Zoloft)	25-50 mg	morning
	paroxetine (Paxil)	10-20 mg	morning or evening
	escitalopram (Lexapro)	5-10 mg	morning
	fluoxetine (Prozac)	10 mg	morning
Serotonin-norepinephrine reuptake Inhibitor (SNRIs)	venlafaxine (Effexor)	37.5-75 mg	b.i.d. (or daily if using XR)
	duloxetine (Cymbalta)	20 mg	daily or b.i.d.
Tricyclic antidepressants (TCAs)	amitriptyline (Elavil)	10 mg	evening
	imipramine (Tofranil)	100 mg	evening
	nortriptyline (Pamelor)	10 mg	evening
	desipramine (Norpramin)	25 mg	evening
Other	bupropion (Wellbutrin)	75 mg	t.i.d. (b.i.d. for SR and daily for XL formulations)
	mirtazapine (Remeron)	7.5-15 mg	evening

BOTTOM LINE: When antidepressant medication therapy is indicated in the elderly, most patients can be initiated on citalopram 10-20 mg a day or sertraline 25-50 mg a day. As part of initiating treatment, patients should be screened for high-risk factors and referred for more immediate treatment if high-risk factors are present.

Following up: duration of therapy, checking for response, augmenting therapy

Patient adherence to medications is a critical concern in the treatment of depression. While non-adherence occurs with all drug classes, it is a particular challenge when treating mood disorders, as the apathy and hopelessness that can be symptoms of depression also reduce interest in treatment. Choosing medications with less risk of side effects and lower cost, such as citalopram and sertraline, can promote better adherence. Discussing medication adherence with patients is a vital part of each reassessment, and reasons for non-adherence should be explored in detail.

Assessing response to treatment

Patients who are started on an antidepressant should be reassessed in 4-6 weeks or sooner for tolerance and efficacy, with specific attention to suicide risk and targeted questions about medication adherence. Patients should be reminded that while side effects can occur early in treatment, they should not expect an immediate benefit from antidepressants. Although some patients begin to feel better within 1-2 weeks, these drugs can require 4-6 weeks to take effect, and potentially up to 12 weeks in elderly patients.⁵⁵ Depending on response, patients should be followed up subsequently at 4-6 week intervals, and then less frequently as the severity of symptoms decreases. Patients without a change in symptoms are defined as “no response” to treatment, while patients who experience some improvement but do not meet the criteria for “adequate response” (defined below) are considered to have “partial response” to treatment.

In general, a 50% reduction of symptoms is considered an adequate response in the first 6 weeks of treatment,¹²⁵ and as noted above, an adequate response can be expected in about 50% of patients treated with antidepressant medications. A patient's response to treatment can be assessed by using a rating scale to follow symptoms over time. One option is the 15-item Geriatric Depression Scale (GDS-15), described earlier. This scale can be given to the patient to fill out in the waiting room (see Appendix 1). Five points or more on

the GDS-15 is considered positive for depression; to assess response, for example, a score going from 6 to 3 would be a reason to stay with the current treatment choice.

An alternative to the GDS is the list of 9 symptoms in the DSM-IV criteria for depression, counting the remaining symptoms after treatment to get a rough estimate of the treatment response. For example, if the patient started out with 8 of the diagnostic criteria, a reduction to 4 symptoms would be considered a response. The gold standard is the Hamilton Depression Scale, a clinician-administered 17-item scale used frequently in research studies that is based on the DSM-IV list of diagnostic criteria,⁵⁶ but this tool is not as practical for routine office use.

Assessing response to Initial Treatment	
Metric	Criteria for adequate response
Geriatric Depression Scale (15 items; see appendix)	50% reduction in score
DSM-IV Depression Criteria (9 symptom domains)	50% reduction in positive symptom domains
"How depressed are you compared to before"	Answer of "much better" approximately equal to measures above

As a less complex assessment tool, clinicians can try to assess response to treatment by asking the patient overall questions about their symptoms, such as:

"How depressed are you now compared to when we first met? Would you say: very much worse, much worse, worse, no change, better, much better, very much better, or don't know?"

Research has demonstrated that when asked in this way, a statement of "much better" provides good sensitivity and specificity to estimate a 50% reduction in depression symptoms.¹²⁵

BOTTOM LINE: Patients beginning antidepressants for depression require careful follow up, with a return visit within 4-6 weeks after initiation. Several tools can be used to assess the response to treatment.

When initial therapy is not effective

If the initial treatment does not result in an adequate response, other strategies can be considered. Decisions should be based on the degree of initial response (partial response vs. no response). For some patients initiated on a low dose of antidepressants and experiencing a partial response, recent large trial

data and practice guidelines suggest that a dose increase may improve symptoms.¹²⁶ For recommended first-line agents (citalopram and sertraline) this would mean doubling the dose and re-evaluating the patient within 4-6 weeks. For patients who either have no response at their first follow up visit or have not achieved an adequate response after a trial of dose escalation, changes in therapy are probably needed. Possible next steps include switching to an alternative medication, augmenting with a second agent, or incorporating psychotherapy into the treatment plan.

Unfortunately, very little research provides guidance on next-step strategies specifically tailored for the elderly. However, one recent practical clinical trial in all-age adults evaluated changes in treatment for patients who did not respond to their initial antidepressant, including some elderly patients.

The **Sequenced Treatment Alternatives to Relieve Depression (STAR*D)** study, published in 2006, was a landmark trial supported by the National Institute of Mental Health of the National Institutes of Health. It aimed to assess multi-step treatment strategies in depression, and included 3,671 patients at 41 U.S. sites.¹²⁷ As a first step, all subjects received citalopram for 12-14 weeks; and 36.8% of subjects experienced remission from depression at a mean dose of 41.8 mg daily.¹²⁷

Subjects not achieving remission entered the second step of the study, in which treatment was either switched or augmented. In the group that were switched (n= 789), patients were randomized to receive either bupropion SR (up to 400 mg per day), sertraline (up to 200 mg per day), venlafaxine XR (up to 375 mg per day), or cognitive therapy for up to 14 weeks.¹²⁸ In the group that was augmented (n=650), subjects were randomized to receive bupropion (up to 400 mg per day), buspirone (up to 60 mg per day), or cognitive therapy, in addition to continuing citalopram. The overall remission rate for the second step was 30.8%. The various treatments were not significantly different in terms of their tolerability or side effects.¹²⁸ Of particular clinical importance, the study found that lack of tolerance or lack of effect with one SSRI did not predict lack of tolerance or lack of effect with another.

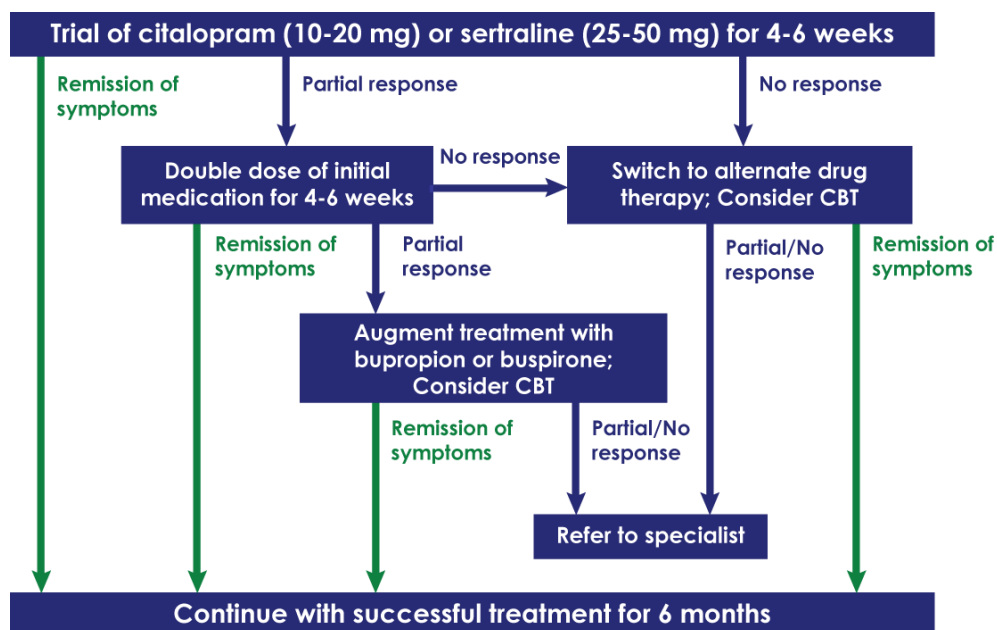
These results suggest that switching to another agent, even in the same drug class, can be a reasonable option after an inadequate response to one drug. In terms of augmentation, improvements were seen with both bupropion and buspirone. Smaller numbers of patients with partial response or no response progressed to the third and fourth phases of the study, for which treatment augmentation included various additional antidepressants, but the remission rates for these phases were lower (13.7% and 13.0% in third and fourth stages respectively).¹²⁷

Although the STAR*D trial included patients of all ages, sub-group analyses did show that event rates and response rates in the older patients were similar to those in the entire population.¹²⁹ Accordingly, these results can be used to guide treatment approaches for patients who do not respond to their initial antidepressant treatment. For patients with non-response, a switch to an alternative medication is recommended; possibilities include other SSRIs, SNRIs, or bupropion. For patients with partial response even after a trial of increased dose of their initial antidepressant, one can follow the approach of STAR-D and augment therapy with bupropion or buspirone. For either switching or augmentation strategies, cognitive behavioral therapy can also be included as a potentially useful option.

Patients who do not achieve a good response after a trial of augmenting or switching treatment should be considered for referral to a specialist for further evaluation and treatment. The evidence from STAR*D showing decreased response rates in the third stage of treatment supports this approach. In addition, specialty referral is appropriate for patients who do not have an adequate response after their first stage of treatment and have either worrisome clinical features (poor appetite, worsening vegetative symptoms) or comorbid conditions complicating the choice of second line medications.

BOTTOM LINE: With appropriate follow up and step therapy, about two-thirds of patients can be treated to remission. Specialty referral should be pursued for patients not responding after a second step in treatment or with worrisome symptoms at any stage in evaluation and treatment.

Figure 7: Management of depression in the elderly



Duration of therapy

When an adequate response is achieved, patients should be treated for at least 6 months and, for those with recurrent depression, at least 12 months.¹³⁰ During this period the patient should be carefully monitored to ensure that the response is sustained. The risk of a recurrent episode of depression after antidepressant discontinuation may be greater in the elderly than in younger adults; for example, one study found that 60% of elderly patients relapsed after discontinuing their antidepressant.¹³¹ As a result, some have argued for elderly depressed patients to remain on antidepressants long-term for maintenance therapy.¹³² For older patients with multiple episodes of depression, chronic maintenance therapy is likely warranted. For most elderly patients, however, adding another chronic medication contributes to polypharmacy and may make it difficult for them to adhere to medications for other conditions.

Accordingly, after an adequate course of treatment, elderly patients treated for depression should have a trial of medication withdrawal. Since rapid discontinuation of medications may cause an acute worsening of symptoms, especially for patients treated with SSRIs, antidepressants should be tapered carefully.¹³³ Specific tapering schedules have not been evaluated in trial settings, but in general a 25% reduction in antidepressant dose every 1-2 weeks should allow for safe withdrawal of the medication. During this time, patients must be monitored carefully for recurrence of symptoms. If symptoms recur, return to the lowest previous effective dose. Some recommend giving patients a second trial of medication tapering after that. In addition to allowing for the discontinuation of medications for patients who successfully complete their withdrawal schedule, a tapering regimen will allow for the lowest possible chronic dose in patients who require maintenance therapy, reducing the risk of adverse events.

BOTTOM LINE: Patients who are treated successfully should be treated for a minimum of 6 months. Withdrawing medication after 6-12 months can reduce the risks of polypharmacy and drug interactions, but some patients with chronic depressive symptoms will require longer-term medication treatment. SSRIs should be tapered to avoid "discontinuation syndrome."

Management of minor depression and dysthymia

Epidemiology of minor depression and dysthymia

Minor depression and dysthymia, defined in earlier sections, are common in the elderly. In one study the prevalence of minor depression among older adults was 1 in 20.¹³⁴ Dysthymia has a lifetime prevalence of 3-6% in all adults, affects approximately 2-4% of the elderly, and is more prevalent than major depressive disorder.^{135, 136} Most of these patients have a late age of onset and limited psychiatric comorbidities compared with younger patients. Therefore, clinical features of dysthymia in the elderly are typically distinct from those of dysthymic disorders in the younger patients. Dysthymia is often associated with other depressive conditions: 75% of people have concurrent disorders such as major depression, anxiety and substance abuse.

Treatment of minor depression (also called subsyndromal depression)

There has been controversy about the optimal management of minor or subsyndromal depression. This is partly because in all-age adults, response to antidepressant treatment has been much weaker in patients with less severe depression.⁵⁷ However, researchers have found that in the elderly, the presentation of depression may be atypical, possibly because they experience or communicate symptoms differently; for example, elderly depressed are less likely to report sadness as a symptom.¹³⁷ Some researchers have suggested that in the elderly, these are significant types of depression; for example, one study found that minor depression was associated with a 1.80-fold higher risk of death in elderly men.¹³⁸ Despite this, there is limited evidence available to guide treatment for minor depression in the elderly. One study compared sertraline and citalopram in the treatment of late-life non-major depression concluding that both may improve depressive symptoms and cognitive function in the non-demented elderly. There are only 2 studies comparing antidepressants with placebo. One study showed treatment benefit with amitriptyline.¹³⁹ A randomized placebo controlled trial examined the role of paroxetine in minor depression. It reported improved mental health functioning only in those patients who were in the lowest tertile of baseline functioning.¹⁴⁰

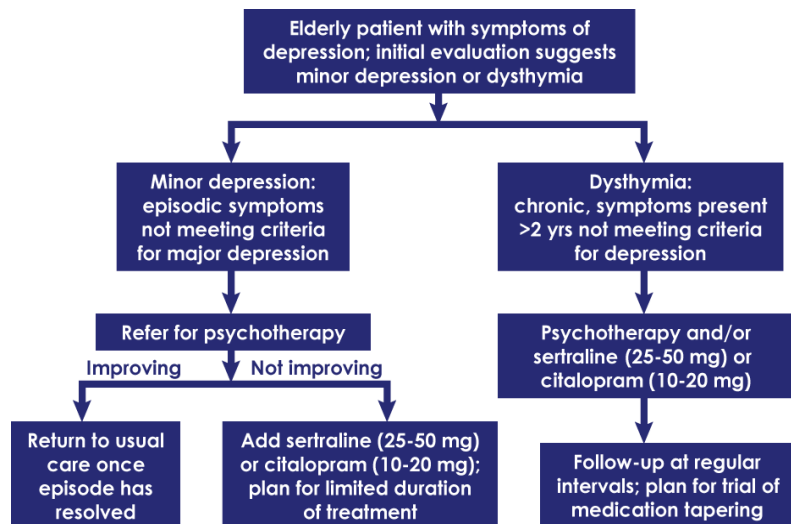
Available guidelines for management of depression in the general population do not advocate for antidepressant therapy for minor depression, given the limited evidence base. Rather, they focus on psychological interventions such as cognitive behavioral therapy or other forms of psychotherapy. Exceptions where pharmacological therapy may have a primary role include patients who have had moderate or severe depression, patients who have not responded to other interventions and patients who have

significant psychosocial or other stressors.¹⁴¹ Psychological interventions should be first line treatment options for minor depression. After this clinicians must carefully consider benefits, costs, and potential side effects of medication treatment for each individual in the context of comorbidities and social and functional limitations. Minor depression is a risk factor for the later development of major depression,¹¹ so patients in whom minor depression is identified should be monitored carefully for worsening depressive symptoms.

BOTTOM LINE: For elderly patients with minor depression, psychotherapy should be considered first-line treatment. Medications may be a reasonable second option.

Treatment of dysthymia

Both pharmacological and non-pharmacological therapies have a role in the treatment of dysthymia, the chronic, lower-level presentation of depression. Limited evidence suggests that combined pharmacotherapy and psychotherapy may be more effective than medication alone in these patients.¹⁴²⁻¹⁴⁷ Most studies evaluating the effectiveness of psychotherapy have been in geriatric patients with major depression, but it does appear to be a promising treatment modality in dysthymia,^{38, 148, 149} especially given the chronic nature of this condition and the problems with adding more chronic medications for older patients. Further studies are clearly needed.



A Cochrane systematic review concluded that antidepressants were more effective than placebo for the treatment of dysthymic patients.¹⁵⁰ In this review of 29 trials, there were differences in illness definition, length and quality of trials, and drugs used, but a consistent effect of antidepressants was noted.¹⁵⁰ Another Cochrane systematic review compared active drugs for the treatment of dysthymia and reported the most robust evidence for TCAs and SSRIs with similar clinical responses, although with different side effect profiles.¹⁵¹ A total of 14 trials were included. Both reviews included patients of all ages and were not specific to the elderly.

Many trials focus on adult patients with major depression and include subclasses of patients with dysthymia.^{152, 153} Several studies specifically examined pure dysthymia in geriatric patients. One study of fluoxetine in geriatric dysthymic patients reported a 50% reduction in Hamilton Depression Score, but included only 23 subjects. A larger randomized double blind placebo controlled trial studied fluoxetine in elderly patients with dysthymia. This study of 90 patients reported limited efficacy of fluoxetine compared to placebo.¹⁵⁴ The largest randomized controlled trial to date, including 211 older dysthymic patients, reported moderate benefit of paroxetine for depressive symptoms and mental health function in elderly patients with dysthymia. An open-label treatment trial of venlafaxine in elderly patients with dysthymia reported remission in 47.8% of study subjects after a 12 week period, but the sample size was only 23.¹⁵⁵

Ultimately both pharmacologic and non-pharmacologic treatments have been shown to be of benefit in dysthymia, and thus a combination of both is probably appropriate. As is the case in treatment of major depression, the anticholinergic properties of TCAs are likely to result in poor tolerability for frail elderly patients, especially with chronic use, and these agents should be avoided.

BOTTOM LINE: For elderly patients with dysthymia, pharmacologic and non-pharmacologic therapy may improve symptoms, but the evidence is limited.

Prescribing antidepressants for other uses

Antidepressant medications have been used for a variety of non-psychiatric conditions, including chronic pain, prevention of headaches, smoking cessation, and various other indications. The clinical evidence for these additional indications is variable. This section reviews the evidence for use of antidepressants in several conditions other than depression. Some of the medication uses described in this section have not been approved by the FDA, so clinicians should use their medical judgment when considering the potential benefits of prescribing antidepressants for the indications below.

Chronic pain

Chronic pain is a common problem, especially as patients live for longer periods of time with chronic diseases. The evidence that antidepressants can help with pain is limited to neuropathic pain, which most commonly appears in elderly patients as diabetic neuropathy or post-herpetic neuralgia.¹⁵⁶⁻¹⁵⁸ These two conditions are the most studied and there is good evidence that TCAs

provide relief for many patients with these types of pain. There are, however, many less common types of neuropathic pain and a wide variety of non-neuropathic pain syndromes for which the evidence regarding treatment with TCAs or other antidepressants is uncertain.

Multiple antidepressant medications have been studied in the treatment of neuropathic pain. Evidence supports the use of tricyclic antidepressants (TCAs) for diabetic neuropathy, but some agents (especially amitriptyline) should be avoided in older patients. Evidence for selective serotonin reuptake inhibitors (SSRIs) in the treatment of neuropathic pain is limited, but data support the use of two serotonin-noradrenaline reuptake inhibitors (SNRIs): duloxetine and venlafaxine.

For other pain syndromes, such as trigeminal neuralgia and centrally mediated pain, there is no evidence for efficacy of antidepressants. Many other medications have been used for neuropathic pain (including gabapentin, pregabalin, non-steroidal anti-inflammatories, opiates). Although full discussion of these agents is beyond the scope of this review, they should be considered carefully for patients who cannot tolerate TCAs, even at low doses.

TCAs

TCAs have been used for neuropathic pain for over 30 years and many studies support their effectiveness as first-line treatment for neuropathic pain caused by diabetic neuropathy or post-herpetic neuralgia.¹⁵⁶⁻¹⁵⁸ Amitriptyline, desipramine, imipramine, clomipramine, and nortriptyline have all demonstrated efficacy when compared to placebo. The number-needed-to-treat (NNT) to achieve improvement in pain (not complete resolution) with these agents is generally between 2 and 4,¹⁵⁸ indicating that 25-50% of patients will have some response to these medications. These numbers also indicate, however, that the majority of patients will not have pain relief with a TCA and will require a second-line agent instead.

Studies for other types of neuropathic pain (such as trigeminal neuralgia) and non-neuropathic pain syndromes (such as centrally mediated pain) have not demonstrated a consistently beneficial effect for TCAs or other antidepressants.^{156, 158}

When studies compared TCAs to other TCAs in the treatment of neuropathic pain, no consistent differences between agents were found,¹⁵⁸ suggesting that all medications in this class could be used. While amitriptyline has the largest volume of evidence showing efficacy, it has a particularly increased risk of side effects (anticholinergic effects such as sedation, dry mouth, blurred vision, as well as less common cardiac complications) in the

elderly.¹⁵⁷ In older patients the secondary amine TCAs (nortriptyline, desipramine) are a better choice as first line treatment.¹⁵⁷

When starting TCAs for neuropathic pain, doses below those for depression should be used. The recommended starting dose is 25 mg, taken at bedtime. Doses can be increased by 25 mg every 3-7 days if the patient is tolerating the medication without side effects. Average final doses in research studies have been about 75-100 mg per day.¹⁵⁷ If patients are not having symptomatic improvement after a 6-week trial of TCAs, it is unlikely that they will work and an alternative agent should be considered. The dosing regimens used for treatment of neuropathic pain are considerably lower than the doses used for primary treatment of depression, reducing but not completely removing the toxicity concerns. Physicians should not assume that a TCA prescribed for pain will provide adequate pharmacotherapy for depression.

Other antidepressants

Studies of selective serotonin reuptake inhibitors (SSRIs) have not demonstrated efficacy for these agents in treatment of neuropathic pain.¹⁵⁹ Duloxetine^{160, 161} and venlafaxine,^{162, 163} both serotonin-noradrenaline reuptake inhibitors (SNRIs), have been studied in patients with diabetic neuropathy and have shown some improvement in pain. The NNTs for these agents were closer to 5, indicating that 20% or fewer of patients improved on these agents.^{156, 158} Accordingly, duloxetine and venlafaxine should be regarded as second-line choices for diabetic neuropathy. They may be reasonable first-line agents for patients who cannot tolerate TCAs. There are no good studies of SNRIs in the treatment of post-herpetic neuralgia.

Patients treated with duloxetine should start on a dose of 30 mg per day, increasing to 60 mg daily after one week with a maximum dose of 60 mg twice daily. For venlafaxine the starting dose is 37.5 mg per day, increasing to twice daily and then by increments of 75 mg per week up to a maximum of 225 mg per day. A total trial of 4-6 weeks of treatment for either of these agents should reveal if they are helping with symptoms.¹⁵⁷

Other agents

Many other medications have been studied for neuropathic pain, including gabapentin, pregabalin, topical lidocaine, non-steroidal anti-inflammatory medications, narcotic analgesics, and others. Detailed discussion of these agents is beyond the scope of this review. In general, these are second-line agents for the treatment of diabetic neuropathy or post-herpetic neuropathy.¹⁵⁶⁻¹⁵⁸

In summary, TCAs can improve symptoms for some patients with neuropathic pain. Careful monitoring for side effects is needed, and amitriptyline should be avoided in older patients. Doses should start at 25 mg and increase slowly. SNRIs (duloxetine and venlafaxine) are second-line agents and may be a good choice for patients who cannot tolerate a TCA. As with TCAs, treatment should start at low doses and increase slowly. If patients are not improving after a 4-6 week trial of treatment, then the medication should be discontinued.

BOTTOM LINE: TCAs have been shown to be effective in the treatment of neuropathic pain. In the elderly, low doses of newer TCAs (nortriptyline and desipramine) should be used to minimize side effects – doses lower than are needed to treat depression.

Sleep

A number of antidepressants, most notably trazodone and amitriptyline, have been used to treat insomnia because of their sedative properties. These medications may be most useful in patients who are also depressed. However, there is little data demonstrating the efficacy of antidepressants in the management of insomnia in patients who are not also depressed.¹⁶⁴ In elderly patients, non-pharmacologic measures should be attempted to treat insomnia first; these patients often experience adverse effects from sleep medications. Sleep hygiene measures, relaxation therapy, cognitive behavioral therapy, and sleep restriction therapy may all offer meaningful benefit, with benefits that may exceed that of medication therapy.¹⁶⁵⁻¹⁶⁸ When used for insomnia in the elderly, trazodone should be started at a dose of 25-50 mg a night, and titrated up 25 mg a week to usual dose of 50–100 mg a night. This is less than the usual dose needed to treat depression (150–600 mg/day in 3 divided doses). Because of its anticholinergic effects, amitriptyline should rarely be used in the elderly for insomnia.

Hot flashes

Antidepressants may play a useful role in the management of hot flashes in post-menopausal women. The selective serotonin reuptake inhibitors (SSRIs) and selective serotonin norepinephrine reuptake inhibitors (SNRIs) have been shown to relieve symptoms from hot flashes, and offer an important alternative to hormonal therapy. RCTs comparing venlafaxine vs. placebo for post-menopausal hot flashes indicate significant reductions in self-reported symptoms (51 versus 15 percent reduction in hot flash score) at a dose of 75 mg/day,¹⁶⁹ and even better at higher doses,¹⁷⁰ although not as effective as progestin,¹⁷¹ and associated with increased risk of side effects such as dry mouth and sleeplessness.¹⁶⁹ Paroxetine at 12.5 or 25 mg/day was found to have similar

effects in placebo controlled randomized controlled trial.¹⁷² Trials evaluating the efficacy of sertraline, fluoxetine and citalopram have not indicated benefit compared to placebo.^{173, 174}

Smoking

The antidepressant bupropion, which acts by increasing central nervous system noradrenergic and dopaminergic function, is prepared as an extended release medication and is the best-studied antidepressant for the management of smoking cessation. In the elderly, treatment is generally initiated with 37.5 mg of immediate release tablets twice daily or 100 mg/day of sustained release tablets, increased by 37.5-100 mg every 3-4 days as tolerated to a maximum dose of 300 mg a day, and continued for 7-12 weeks.

A Cochrane meta-analysis of randomized controlled trials evaluating the effect of bupropion on smoking cessation rates indicate an approximate doubling of cessation rates when compared to placebo, both immediately after therapy and at follow up one year later.¹⁷⁵ There is mixed data regarding whether there is any marginal benefit of using bupropion in addition to nicotine replacement over bupropion alone.^{175, 176} Studies of nortriptyline indicate similar improvements to bupropion in rates of cessation.¹⁷⁵ However, there is far less data with regard to nortriptyline, and it causes greater side effects, leading the Agency for Healthcare Research and Quality (AHRQ) to consider it a second-line agent in its guidelines.¹⁷⁷ The Cochrane meta-analysis did not find evidence to support the use of MAO-inhibitors, SSRIs or SNRIs for smoking cessation.

More recent data suggests that varenicline (Chantix) is the most effective pharmacologic therapy and may be used as first line therapy.¹⁷⁸ Bupropion may be a better option for smokers who are also depressed. Bupropion may cause dry mouth and insomnia, and seizures occur in approximately 0.1% of patients; these concerns may be exacerbated in an elderly population with more comorbidities and polypharmacy.

Headaches

Antidepressants are also used to prevent both tension type and migraine headaches. Tricyclic antidepressants, specifically amitriptyline, are a mainstay of preventive therapy for tension type headaches. A meta-analysis of the effects of antidepressants in tension type headaches indicated a reduction in headache duration by 1.26 hours per day (95% CI 0.06-2.45) with TCAs, while there was no beneficial effect of SSRIs.¹⁷⁹ Doses of 10 or 12.5 mg at night are recommended at initiation, with slow titration upwards to limit adverse effects which may be severe in elderly patients. There is limited data evaluating the efficacy of SNRIs in tension type headache prevention.

Similarly, a meta-analysis of the use of antidepressants in migraine headache indicated a doubling of the rate of symptomatic improvement when compared to placebo.¹⁸⁰ Amitriptyline is the best studied of the antidepressants. Considering the high rate of side effects in the elderly, and the numerous other therapeutic options that may be more tolerable, antidepressants should be considered for migraine prophylaxis in the elderly who are non-responsive to alternate treatments or who suffer from depression.

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Appendix 1:

Geriatric Depression Scale (GDS) Short Form		
Choose the best answer for how you have felt over the past week:		
1. Are you basically satisfied with your life?	Yes	No
2. Have you dropped many of your activities and interests?	Yes	No
3. Do you feel that your life is empty?	Yes	No
4. Do you often get bored?	Yes	No
5. Are you in good spirits most of the time?	Yes	No
6. Are you afraid that something bad is going to happen to you?	Yes	No
7. Do you feel happy most of the time?	Yes	No
8. Do you often feel helpless?	Yes	No
9. Do you prefer to stay at home rather than going out and doing new things?	Yes	No
10. Do you feel you have more problems with memory than most?	Yes	No
11. Do you think it is wonderful to be alive now?	Yes	No
12. Do you feel pretty worthless the way you are now?	Yes	No
13. Do you feel full of energy?	Yes	No
14. Do you feel that your situation is hopeless?	Yes	No
15. Do you think that most people are better off than you are?	Yes	No

Scoring for the Geriatric Depression Scale

- Score 1 point for every "yes" in questions 2,3,4,6,8,9,10,12,14,15
- Score 1 point for every "no" in questions 1,5,7,11,13

A total score greater than 5 suggests the need to see a doctor.

If you have any concerns about your response, call the doctor for further testing. There is a good reason to seek medical help. There are many effective ways to treat depression in older adults.

Source: Sheikh, J.I., and Yesavage, J.A. Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clinical Gerontologist* 5(1-2): 165-173, 1986