

# Evidence-Based Pharmacologic Interventions for Geriatric Depression

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Geriatric depression is a growing public health problem [1,2]. The estimated prevalence of geriatric major depression in the general population is 1% to 2% [3,4]. Depressive symptoms not meeting the criteria for major depression occur in approximately 15% of older adults [5]. The prevalence of major depression in community-dwelling older adults is 1% to 3%, but the prevalence is at least 10% to 12% in primary care and hospital inpatient settings [6]. Despite the common prevalence of depression in older adults, late-life depression is often under-recognized and under-treated, particularly in nonpsychiatric settings [4].

Major depression is a leading cause of disability in adults [7]. In elderly patients, both depression and medical illness have an additive effect on disability and lead to an increase in mortality and nursing home placement [8,9]. Depression severity is a predictor of variance in instrumental activities of daily living [10]. The mechanisms linking depression and disability are still unclear, but it appears that the depressed state itself can be disabling, and depression increases the disability caused by chronic medical conditions [11]. Bruce and colleagues [12] have described a mutually reinforcing, downward-spiraling relationship between depression and disability. In contrast, treatment that results in a reduction in the severity of depression leads,

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1 year later, to a reduction of approximately 50% in the number of days burdened by disability.

A review of the evidence for the treatment of geriatric depression must be considered in the context of the considerable heterogeneity of late-life depression that inevitably complicates treatment outcomes. Recent attention has focused on the impact of underlying structural brain abnormalities and the presence of comorbid disorders as major factors affecting treatment response.

### **Cognitive impairment and structural abnormalities**

Late-life depression is associated frequently with cognitive impairment [13] and may present with structural brain abnormalities such as ventriculomegaly and white-matter hyperintensities [14]. Structural brain abnormalities may define a subgroup of depressive disorders that are less likely to respond to treatment interventions. Preliminary findings suggest that white-matter microstructural abnormalities lateral to the anterior cingulate may be associated with a low rate of remission [15]. These underlying processes are an example of one of the many factors that may be associated with finding that major depression developing later in life tends to be more chronic and less amenable to treatment [14].

### **Psychiatric comorbidity**

Co-occurring psychiatric disorders are also associated with poorer treatment responses to standard treatment for geriatric depression. The prevalence of anxiety disorders in elderly depressed patients is 10% to 20% [16,17]. Comorbid anxiety disorders are associated with decreased social functioning and increased somatic symptom severity [16]. Personality disorders co-occur with late-life depression or dysthymia 10% to 30% of the time. Patients with comorbid personality disorders are likely to have an onset of depression at an earlier age and multiple recurrent depressive episodes [18]. Elderly patients with major depression also have a three- to fourfold higher risk of having a comorbid alcohol use disorder compared with non-depressed elders [18]. These disorders are relatively common in older persons with depression and are associated with poorer treatment outcomes.

### **Medical comorbidity**

Comorbid medical disorders are common among older adults with depression and complicate treatment response and outcomes. Medical illness is a risk factor for the development or worsening of depression, and depression itself is a risk factor for medical illness [19]. Depression in patients with chronic physical problems leads to a worsening of disability, higher rates of

hospitalization and nursing home admission, and premature mortality [8,20–23]. Examples of comorbid medical disorders complicating the course and treatment outcome of geriatric depression include cardiovascular disease, cerebrovascular, endocrine, neurologic, and joint and connective tissue disorders, malignancy, and immunodeficiency disorders.

A substantial literature documents the complex relationship between depression and cardiovascular disease and between depression and cerebrovascular disease or stroke. Co-occurring depression has been associated with worse medical outcomes. For example, depression in cardiac patients is associated with a greater number of re-hospitalization days after angioplasty or coronary artery bypass grafting [24] and greater long-term mortality after myocardial infarction [25]. Co-occurring depression and treatment outcomes have also been associated with the type and location of vascular disease. For example, approximately 20% to 30% of post-stroke patients develop either minor or major depression. Left-sided stroke is more likely to lead to early onset ( $\leq 3$  months) post-stroke depression, whereas right-sided stroke is more likely to lead to later-onset depression [26]. Depression after stroke is associated with cognitive impairment, especially when the lesions are left-sided [27]. Although there is only a limited literature on the treatment of post-stroke depression in geriatric patients, preliminary results are promising with respect to the prevention of relapse by early treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants. For example, in a study of elderly post-stroke patients receiving fluoxetine or placebo for 3 months, the fluoxetine group had fewer depressive relapses compared with the placebo group within 3 to 18 months after stroke [28].

The association between endocrine disorders and depression in older adults is also well documented. For example, diabetes doubles the risk of comorbid depression [29]. Depression is also associated with poor treatment outcomes for diabetes. Depressed diabetics are less likely to adhere to dietary and medication recommendations than nondepressed diabetics are, and they use more medical and mental health services [30]. Hypothyroidism in the elderly has a prevalence rate of 5% to 20% in women and a prevalence rate of 3% to 8% in men [31]. Both overt and subclinical hypothyroidism is associated with depression [32]. However, diagnosis and treatment are complicated by the overlapping symptoms associated with both depression and hypothyroidism. For example, the symptoms of hypothyroidism include fatigue, psychomotor retardation, constipation, and mild weight gain. Similarly, common treatments for hypothyroidism can directly and indirectly affect the symptoms of depression, confounding assessments of treatment response.

Neurologic disorders that affect motor function are also associated with high rates of affective disorders in older adults. For example, Parkinson's disease has a rate of comorbid depression ranging from 40% to 50% [33]. Symptoms common to the two disorders are apathy, concentration and memory difficulties, and attention deficit. Patients with Parkinson's disease experience higher levels of dysphoria, irritability, and pessimism than

individuals who are not suffering with the disorder [26]. The frontal lobe and basal ganglia dysfunction characteristic of Parkinson's disease may contribute to the development of depression in these patients, as do psychosocial factors such as social isolation and disability [33]. Multiple sclerosis is increasingly common in the elderly as treatment advances prolong survival. The prevalence of depression can be as high as 20% among patients with multiple sclerosis. The rate of completed suicide is over seven times that of the general population [26]. Lesions in the left anterior temporal and parietal regions have been associated with depression [34].

In addition to cardiovascular, cerebrovascular, endocrine, and neurologic disorders, other conditions that increasingly affect older adults have demonstrated associations with depression and treatment outcomes. Associations have been clearly documented between depression and a variety of disorders, including joint disease, connective tissue disorders, malignancy, and more recently, immunodeficiency disorders.

For example, fibromyalgia is a condition characterized by persistent diffuse pain, stiffness, fatigue, tender points, mood disturbances, and nonrestorative sleep. This illness occurs mainly in women, and the frequency increases with age. The prevalence of fibromyalgia in women between the ages of 60 and 79 years old is 7% to 10% [35,36]. Over half of the patients with fibromyalgia have major depressive disorder [37]. Pancreatic cancer is also a disease associated with aging, with a mean age of onset of 65 years [38]. Symptoms of depression and anxiety may sometimes precede the cancer diagnosis [39,40]. Finally, 11% of all AIDS cases reported annually in the United States are older than 50 years of age [41]. Depression has been directly associated with a decrease in the numbers of natural killer and CD8 cells, which normally inhibit viral activity and are indirectly linked to HIV disease progression because of nonadherence with antiretroviral therapy [19].

In summary, the co-occurrence of depression with medical disorders is common in older adults and frequently affects the course and outcomes of treatment of both the psychiatric and medical disorders. Comorbidity is a cardinal feature of geriatric depression and is relevant to considering variations in the effectiveness of treatment observed in older adults. Hence, any conclusions about the overall efficacy or effectiveness of different treatments should always be considered in the context of the individual patient presentation when making a treatment decision. With this as background for interpreting treatment effectiveness, this review addresses the pharmacologic management of depressive illness in the elderly and the evidence base supporting treatment interventions for geriatric depression.

## Methods

Randomized controlled trials, systematic reviews, meta-analyses, and evidence-based reviews were identified by a search of medical literature

databases, MEDLINE, EMBASE, and PsychINFO, and selected expert consensus guidelines. A classification scheme was used to categorize the level of evidence for specific treatment recommendations based on a letter grade A, B, C or D (Box 1), summarizing the data supporting the recommendation [42]. This classification approach is used in highlighting the results. Some interventions were assigned a grade C or D recommendation as evidence from meta-analysis of randomized controlled trials (grade A) is not available for all the pharmacologic interventions identified in this review.

In conducting this review, meta-analyses and systematic reviews were identified that summarize the evidence of the comparative efficacy and tolerability of tricyclic antidepressants (TCAs) and SSRIs in geriatric depression. Then, treatment trials restricted to older adults for SSRI and novel non-SSRI antidepressants were identified. Finally, the treatment literature and associated recommendations were reviewed for important clinical issues associated with the pharmacotherapy of geriatric depression, including maintenance treatment and relapse prevention, treatment of psychotic

### **Box 1. Categories of evidence and strength of recommendations**

#### *Category of evidence*

la-evidence from meta-analysis of randomized controlled trials

lb-evidence from at least one randomized controlled trial

IIa-evidence from at least one controlled study without randomization

IIb-evidence from at least one other type of quasi-experimental study

III-evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies

IV-evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

#### *Strength of recommendation*

A-directly based on category I evidence

B-directly based on category II evidence or extrapolated recommendation from category I evidence

C-directly based on category III evidence or extrapolated recommendation from category I or II evidence

D-directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

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From Shekelle PG, Woolf SH, Eccles M, et al. Clinical guidelines: developing guidelines. *BMJ* 1999;318(7183):593-6; with permission.

depression, and the use of electroconvulsive treatment. This review focuses on recent geriatric studies examining the comparative efficacy of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs). The reader is referred elsewhere to recent meta-analyses [43–46] and systematic reviews [47–49] for comprehensive assessments of the effectiveness of TCAs and other agents in the treatment of geriatric depression [46].

## Results and meta-analyses

The evidence base supporting different treatment strategies for geriatric depression is illustrated in Table 1. As shown, category I evidence supports the use of antidepressants alone or in combination with psychotherapy in the treatment of geriatric major depressive disorder. The combined use of antidepressants and psychotherapy, antidepressants alone, or psychotherapy alone in the treatment of mild depression is also supported by category I evidence. Table 2 [43,45,46] shows results of meta-analyses comparing the effectiveness of tricyclic antidepressants and selective serotonin reuptake inhibitors in geriatric depression.

As shown, SSRIs and TCAs have comparable efficacy [15,45] and tolerability [45] (see Table 2). Of note, two of the meta-analyses are not restricted to older patients and found different types of side effects and a possible difference in efficacy favoring tricyclic antidepressants in inpatients. However, the most recent meta-analysis conducted by Wilson and Mottram [48] was restricted to studies of older depressed patients and found comparable efficacy and tolerability comparing TCAs with SSRIs.

## Geriatric depression and selective serotonin and serotonin-norepinephrine reuptake inhibitor treatment trials

Table 3 [50–56] provides a summary of selected antidepressant trials for older adults consisting of SSRIs and SNRIs. These studies include 5 randomized controlled trials and two open-label studies. Overall, findings from these studies support an evidence base for the efficacy of these agents

Table 1  
Treatment strategies in geriatric major depression

Intensity	Treatment strategy (A, D)
Major depression	Antidepressant alone Antidepressant and psychotherapy
Mild depression	Antidepressant and psychotherapy Antidepressant alone or psychotherapy alone

A, directly based on category I evidence; D, directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence.

Table 2  
SSRIs and TCAs have comparable efficacy (A)

Study	Sample size	Type	Comments
Wilson and Mottram 2004 [46]	11 randomized controlled trials; 537 TCA recipients; 554 SSRI recipients	Meta-analysis	TCA-related drugs are comparable to SSRIs in terms of tolerability and may offer an alternative when SSRIs are either contraindicated or clinically unacceptable
Steffens et al 1997 [45]	36 randomized controlled trials; 4076 patients; 995 SSRI recipients; 973 TCA recipients	Meta-analysis	SSRIs resulted in significantly more gastrointestinal problems and sexual dysfunction, whereas treatment with TCAs produced significantly more complaints of sedation, dizziness, and anticholinergic symptoms
Anderson 2000 [43]	102 randomized controlled trials; 10,706 patients	Meta-analysis	Overall efficacy between the two classes is comparable, but SSRIs are not proven to be as effective as TCAs in in-patients and against amitriptyline; SSRIs have a modest advantage in terms of tolerability against most TCAs

A, directly based on category I evidence.

in the treatment of geriatric depression compared with placebo or compared with other SSRI or TCA treatments.

### Maintenance treatment and relapse prevention

Treatment outcomes for depression include acute phase outcomes, long-term maintenance, and relapse prevention. As shown in Table 4 [57–59], a variety of different outcomes has been defined to evaluate the treatment effectiveness. The prevention of relapse and recurrence is an important goal in the treatment of geriatric depression because of the potentially chronic and disabling nature of the disorder. The goal of maintenance treatment is to prevent recurrence. This phase begins at the end of the continuation treatment when the patient has entered remission. Executive dysfunction has been associated with relapse and recurrence of geriatric major depression [60]. In a study of treatment for major depression, depressed older adults were randomly assigned to receive nortriptyline, placebo, interpersonal psychotherapy (IPT), or IPT with nortriptyline. In the 3-year follow-up period, the group maintained with combined IPT, and nortriptyline had the lowest recurrence rate (20%) compared with placebo (90%) and was superior in preventing or delaying recurrence [61]. Maintenance treatment is recommended for 12 months after a single episode of depression for older adults and from 1 to 3 years for patients with recurrent depression [62].

Table 3  
Selected antidepressant trials (A, B)

Study	Sample size	Age (y)	Dosages (mg)	Type	Scales	Duration (wk)	Comments
Citalopram Karlsson et al 2000 [50]	336	≥ 65	20–40	RCT	MADRS	12	Well tolerated; not sedating for elderly depressed patient with or without dementia
Fluoxetine Koran et al 1995 [51]	671	≥ 60	20	RCT	HAM-D	6	43% response
Paroxetine Cassano et al 2002 [52]	242	≥ 65	20–40	RCT	HAM-D	52	Comparable to fluoxetine
Sertraline Bondareff et al 2000 [53]	210	≥ 60	50–150	RCT	HAM-D	12	Comparable to nortriptyline
Duloxetine Wohlrreich et al 2004 [54]	101	≥ 65	80–120	Open label	HAM-D	52	Well tolerated; effective and safe in the long-term treatment of MDD
Nelson et al 2005 [55]	90	≥ 55	60	RCT	HAM-D	9	30% remission for duloxetine vs 13% for placebo; significant reduction in pain compared with placebo
Venlafaxine Dierick 1996 [56]	116	≥ 65	25–150	Open label	CGI, MADRS	52	67% of patients achieved clinical response by 2 mo

*Abbreviations:* CGI, Clinical Global Impression; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale; RCT, randomized controlled trial.

A, directly based on category I evidence; B, directly based on category II evidence or extrapolated recommendation from category I evidence.

Table 4  
Definitions of treatment outcomes

Results	Definition
Improvement	Residual symptoms [57]
Response	50% reduction in symptoms [58]
Remission	Asymptomatic state usually defined as $\leq 7$ on the HAM-D
Relapse	Increase in depressive symptoms to a syndromal level within 6 mo from remission [59]
Recurrence	A new episode of major depression 6 mo after remission
Resistance	No response or partial response to adequate treatment with two or more antidepressants

*Abbreviation:* HAM-D, Hamilton Rating Scale for Depression.

### Treatment of psychotic depression

Psychotic depression occurs in approximately 20% to 45% of hospitalized depressed elderly [63]. One of the earliest treatment studies for psychotic depression (not specific to older adults) resulted in the recommendation that psychotic depression should be treated with amitriptyline and perphenazine [64]. A subsequent randomized study demonstrated that the addition of a moderate dose of perphenazine to nortriptyline was well tolerated but did not improve efficacy [65]. Studies in mixed age adults have found the SSRIs fluvoxamine, paroxetine, and sertraline and the SNRI venlafaxine to be effective in treating psychotic depression [66,67]. Studies of SSRIs alone or in combination with antipsychotic drugs are lacking in the treatment of geriatric psychotic depression. In the absence of empirical data specific to older adults, geriatric expert consensus guidelines suggest the use of a combination of antidepressant and antipsychotic medications or electroconvulsive treatment (ECT) [62]. These guidelines suggest that the SSRIs and venlafaxine are considered first-line agents, with TCAs a high second-line alternative. Atypical antipsychotics were preferred over traditional antipsychotics in these expert consensus guidelines, with risperidone, olanzapine, and quetiapine rated as the first-line choices [62].

### Treatment with electroconvulsive therapy

ECT has been found to be highly effective in moderate to severe depression and depression with melancholic features [68]. ECT has been recommended as an initial treatment in patients who have depression with psychotic symptoms or catatonia, severe depressive symptoms and functional impairment, and comorbid medical problems, and when there is an urgent need for response (ie, patients who are acutely suicidal or patients who refuse food and are nutritionally compromised). However, depressed

older adults who respond to ECT are at a high risk for relapse unless they receive continuation or maintenance pharmacotherapy or ECT [69]. In a study of patients who underwent ECT because pharmacotherapy failed, patients treated with nortriptyline and lithium had a lower rate of relapse compared with those treated with nortriptyline alone [69].

## Discussion

Effective and well-tolerated treatments for late-life depression exist, including antidepressants, psychotherapy, and electroconvulsive therapy. Treatment outcomes include the reduction of depressive symptoms and suicidal ideation, improvement of cognitive and functional status, and prevention of relapse and recurrence. More than half of the elderly patients treated with antidepressants experience treatment response, defined as a 50% reduction in depressive symptoms [45,58]. In intent-to-treat analyses, the response rates to antidepressants are 50% to 65% compared with 25% to 30% on placebo in randomized controlled trials [5,70,71].

Expert consensus recommendations suggest that older adults tolerate SSRIs better than TCAs [59], although empirical studies reveal similar tolerability and rates of side effects. However, the consequences of the side effects may be more serious for TCAs compared with SSRIs. SSRIs are associated with higher rates of nausea, loss of appetite, and sexual dysfunction, but they have less anticholinergic and cardiovascular side effects compared with TCAs [45]. Patients with pre-existing bundle branch block who are treated with TCAs may develop second degree block [72]. The choice among different SSRIs may be guided by the absence of drug interactions, simplicity of dosing, and side-effect profile. The various SSRIs have similar efficacy, and some (escitalopram, citalopram, and sertraline) have a lower potential for drug interactions.

A partial response to treatment is not uncommon in the treatment of geriatric depression, with the result that clinicians prescribe additional agents in the context of augmentation therapies. Augmentation strategies are added early in treatment to accentuate the clinical response, around 4 to 6 weeks of standard antidepressant treatment for patients who have limited improvement [73]. In patients who experience a partial response to treatment, some clinicians combine antidepressants in the hope of realizing synergistic effects. The combination therapy of two antidepressants has not been studied systematically. Hence, there is no empirical evidence base supporting either the effectiveness or lack of effectiveness for augmentation strategies. However, the common occurrence of partial treatment response after several trials of monotherapy has stimulated the development of expert consensus recommendations for partial treatment response in geriatric depression [52]. These expert consensus guidelines suggest that if there is a partial response after the initial antidepressant treatment to (1) SSRI, then add bupropion, lithium, or nortriptyline; to (2) TCA, then add lithium or SSRI;

to (3) bupropion SR, then add SSRI or lithium; or to (4) venlafaxine, then add lithium [62]. Discontinuing the augmentation treatment may put patients at an increased risk of relapse. In one study [74], patients who received brief augmentation during an acute phase had a 52% relapse rate on follow-up. If there is little or no response to an initial SSRI treatment, the experts support switching to venlafaxine or bupropion [62]. Other suggestions are, if there is no response to TCA, then switch to venlafaxine or SSRI; if there is no response to venlafaxine, then switch to SSRI.

Other important clinical issues in the treatment of geriatric depression include the identification and treatment of the older adult with active suicidal ideation or other signs of increased suicide risk. In industrialized countries, men aged 75 years and older have the highest suicide rate among all age groups [75]. Risk factors for suicide in the elderly include physical illness [76], persistent pain [77], mood disorders [78], alcohol abuse [79], anxiety [80], bereavement, and social isolation [81]. More often, among elderly patients, it has been shown that hopelessness best predicts suicidal ideation in the presence of moderate or higher levels of depressive symptoms [82]. Predictors of suicide attempts include previous suicide attempts with serious intent and severity of depression [83]. Elderly patients who have attempted suicide tend to have higher levels of hopelessness even after successful treatment for depression [84]. The use of firearms is the most common method of completed suicide among older adults [85].

Treatment with an antidepressant medication, usually an SSRI or SNRI, is the mainstay of treatment of a depressed suicidal older adult. An examination of double-blind studies does not demonstrate a causal relationship between pharmacotherapy and the emergence of suicidality [86]. In one retrospective analysis [87], depressed patients treated with fluoxetine ( $n = 1765$ ) were compared with a tricyclic antidepressant ( $n = 731$ ) or placebo group. There was no increased risk of emergence of suicidal ideation among depressed patients treated with fluoxetine.

## Summary

Late-life depression is under-recognized and undertreated in older adults. Depressed older adults who are at an increased risk or undertreatment include patients older than 85 years, those with comorbid medical conditions, and older adults with cognitive impairment receiving home health care or living in nursing homes. Although the existing empirical treatment literature is limited, the available published treatment studies and expert consensus recommendations find that antidepressants are effective. In general the SSRIs and SNRIs pose a low risk for the most serious side effects. Treatment of psychotic depression has not been adequately investigated in older adults, although common practice includes treatment with an SSRI or SNRI in conjunction with an atypical antipsychotic. Treating with antidepressants

augmented by psychotherapy can minimize relapse and disability in depressed patients. Continuation and maintenance treatment at an adequate dose and for an adequate length of time is critical in minimizing relapse. Empirical trials are needed that evaluate the selection and effectiveness of pharmacologic combination therapy and other treatment strategies for treatment resistant and partially responsive major depressive disorder in older adults.

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