

# Management of Depression in Older Adults

## A Review

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**IMPORTANCE** Depression in older adults is a common psychiatric disorder affecting their health-related quality of life. Major depression occurs in 2% of adults aged 55 years or older, and its prevalence rises with increasing age. In addition, 10% to 15% of older adults have clinically significant depressive symptoms, even in the absence of major depression.

**OBSERVATIONS** Depression presents with the same symptoms in older adults as it does in younger populations. In contrast to younger patients, older adults with depression more commonly have several concurrent medical disorders and cognitive impairment. Depression occurring in older patients is often undetected or inadequately treated. Antidepressants are the best-studied treatment option, but psychotherapy, exercise therapy, and electroconvulsive therapy may also be effective. Psychotherapy is recommended for patients with mild to moderate severity depression. Many older patients need the same doses of antidepressant medication that are used for younger adult patients. Although antidepressants may effectively treat depression in older adults, they tend to pose greater risk for adverse events because of multiple medical comorbidities and drug-drug interactions in case of polypharmacy. High-quality evidence does not support the use of pharmacologic treatment of depression in patients with dementia. Polypharmacy in older patients can be minimized by using the Screening Tool of Older Persons Prescriptions and Screening Tool to Alert doctors to Right Treatment (STOPP/START) criteria, a valid and reliable screening tool that enables physicians to avoid potentially inappropriate medications, undertreatment, or errors of omissions in older people. Antidepressants can be gradually tapered over a period of several weeks, but discontinuation of antidepressants may be associated with relapse or recurrence of depression, so the patient should be closely observed.

**CONCLUSIONS AND RELEVANCE** Major depression in older adults is common and can be effectively treated with antidepressants and electroconvulsive therapy. Psychological therapies and exercise may also be effective for mild-moderate depression, for patients who prefer nonpharmacological treatment, or for patients who are too frail for drug treatments.

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Late-life depression is a common psychiatric disorder that diminishes older people's quality of life.<sup>1</sup> Nearly 14% of people older than 55 years have depression including 2% with major depression.<sup>2</sup> The *Diagnostic and Statistical Manual for Mental Disorders* (Fifth Edition) (*DSM-5*) criteria for establishing a diagnosis of a major depressive episode is presented in the Box.<sup>3</sup> For major depression, at least 5 symptoms should be present nearly every day during the same 2-week period. For minor depression or depressive episode with insufficient symptoms according to the *DSM-5*, at least 2 symptoms should be present including depressed affect, for at least 2 weeks. Based on the number of criterion symptoms (Box), the severity of these symptoms, and the degree of functional disability, the *DSM-5* specifies mild, moderate, or severe depression.

Although major depression is less prevalent than in younger individuals, for whom 12-month prevalence estimates for major depression was 6.6% (95% CI, 5.9%-7.3%) based on the National

Comorbidity Survey Replication,<sup>4</sup> its prevalence increases substantially among patients older than 85 years, in hospitals, and in nursing homes.<sup>5-7</sup> Factors associated with late-life depression include female sex, chronic somatic illness, cognitive impairment, functional impairment, lack of close social contacts, personality traits, stressful life-events, and a history of depression.<sup>8,9</sup>

Treating depression in older patients is approached in the same way as it is for younger patients. The mainstay treatments are antidepressants and depression-specific psychotherapies such as cognitive therapy and interpersonal therapy. Establishing a diagnosis of depression in older patients can be more difficult than for younger patients because of physical comorbidities and cognitive dysfunction. The intent of this review is to provide guidance for how to manage depression in frail older patients who take several medications. This review emphasizes the use of both medical and evidence-based psychotherapy for treating depression in older adults.

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**Box. Diagnostic Criteria for Major Depressive Episode According to DSM-5 Criteria<sup>a</sup>**

Five (or more) of the following symptoms should be present nearly every day during the same 2-week period:

- Depressed mood
- Markedly diminished interest or pleasure in (almost) all activities
- Significant weight loss or decrease or increase 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, suicidal ideation, or a suicide attempt or a specific plan for committing suicide.

<sup>a</sup> The symptoms represent a change from previous functioning and cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. At least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. This list is adapted from the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*).<sup>3</sup>

## Methods

### Literature Search

The PubMed database was searched for articles in peer-reviewed journals from inception through January 2017 using MeSH terms: *depressive disorder* and *aged* and *review* or *meta-analysis*. In addition, we searched the Cochrane Library database for depression in older people, also using different terms (for example: *depression*, *depressed*, *depressive disorder*, *depressive illness*). The PubMed search identified 1603 unique articles. The titles and abstracts were examined for relevance, and relevant articles were also screened for references. In addition, we searched the internet for guidelines on the treatment of depression in older people.

## Assessment and Diagnosis

Generally, depression presents with similar symptoms in both older and younger patients.<sup>10</sup> Although there may be minor differences in presentation, the *DSM-5* criteria for establishing a diagnosis of depression is the same for older and younger patients. When seen in primary care, a depressed older patient's chief complaint may not be that of having a depressed mood, rather he/she may present with physical complaints such as fatigue; weight loss; pain; multiple unexplained medical symptoms; memory complaints; social withdrawal; the refusal to eat, drink, and use medication; problems with self-care; and new or increasing use of tranquilizing medication or alcohol. Patients may not associate these symptoms with depression but clinicians must have a high index of suspicion that depression is the underlying cause for these complaints of older patients.<sup>3</sup>

### Evaluation of the Patient With Suspected Depression

When depression is suspected, all 9 symptoms of major depression should be assessed (Box), including suicidality. Suicide is not an easy

topic to discuss, but talking openly about it is beneficial. Patients can respond if asked if they have thoughts of death, wish to be dead, or even have a specific suicide plan. In addition, the duration and severity of the depressive symptoms, associated social and functional impairment, history of depressive and manic episodes, alcohol or other substance abuse, and the presence of cognitive dysfunction and psychotic symptoms should be assessed. Because some older adults underreport depressive symptoms, which in part may be due to memory problems, an interview with a caregiver may be necessary as an adjunct to diagnose depression.<sup>11</sup> Screening for depression or assessing its severity is possible with rating scales, such as the Geriatric Depression Scale (GDS) or the Patient Health Questionnaire 9 (PHQ-9).<sup>12-14</sup> Both scales are examples of self-rating scales in response to which patients have to rate the presence or frequency of a range of depression symptoms. In addition, ratings scales are helpful for monitoring the effectiveness of ongoing treatments and ensuring that the ultimate treatment goal of remission is achieved. (Supplement 1). In older adults, all the medications a patient is taking should be carefully reviewed because medications prescribed for somatic illnesses can induce or worsen depressive symptoms or depression itself.<sup>15</sup> There is no consensus on which laboratory tests should be obtained when evaluating depression in older patients. In general blood counts, glucose level, thyroid-stimulating hormone), and serum levels of vitamin B<sub>12</sub> and folate are advisable.<sup>16</sup>

Cognitive assessment should always be part of routine evaluation of older adults because depression in this age group is often associated with cognitive impairment. The Mini-Mental State Examination is the most widely used screening test for cognitive dysfunction.<sup>17</sup> For patients with complex comorbidities, multimorbidity, frailty, or polypharmacy, a comprehensive geriatric assessment should be performed. A comprehensive geriatric assessment is a systematic evaluation of frail, older persons by a team of health professionals that evaluates multiple issues, including cognition, mood, functional capacity, fall risk, polypharmacy, nutrition, and social support. Comprehensive geriatric assessments are intended to develop a coordinated and integrated plan for treatment and long-term follow-up. These assessments are effective in improving survival and function in older persons and can also reduce polypharmacy.<sup>18,19</sup>

## Pharmacological Treatment

### General Considerations

Late-life depression is often inadequately treated, with a majority of patients receiving no treatment at all, receiving lower than recommended doses of antidepressants, or being treated for too brief a period.<sup>20,21</sup> A systematic review and meta-analysis<sup>22</sup> that included 12 observational studies and involved older patients with depression—only 4% to 37% of whom had received at least some treatment—either living in the community or being treated in primary care, found that after a 2-year follow-up, 33% were well, 33% were depressed, and 21% had died. This means that without treatment, prognosis for depression in older patients is poor. Direct comparisons of different treatments for depression between the older and younger adults have not been published. Comparison with middle-aged patients found little difference in remission rates, but relapse rates appear to be higher among older adults.<sup>23</sup> These observations were mostly made in observational studies.

In these retrospective studies, older adults who were inadequately treated for depression appear to have a worse prognosis than their younger counterparts.

Depression may exacerbate the clinical manifestations of comorbid medical conditions such as diabetes or hypertension and is a risk factor for poor outcomes of these conditions.<sup>15</sup> Recent life events, coping with functional impairment, or having a lack of social contacts are examples of psychosocial factors that are frequent contributors to depression among older adults and should be addressed as part of treatment planning.<sup>15</sup> The complexity of these many conditions is best managed by a multidisciplinary team of clinicians including mental health consultation and intervention combined with primary care management or community-based outreach and monitoring of care.<sup>15,24</sup> Older individuals may not be adequately adherent to recommended treatments because of their cognitive status, medical comorbidities, and problems related to the complexity of polypharmacy.<sup>25</sup> Family member involvement in the care of older patients can facilitate treatment adherence and may lead to improving depression.<sup>24</sup>

### Antidepressants vs Placebo

In general, studies have shown that antidepressants are better than placebo for treating depression (Table 1).<sup>26-36</sup> The response or remission rates in older adults are similar to those of younger adults. In a large meta-analysis that included 51 randomized clinical trials (RCTs) involving patients 55 years or older, 1262 out of 2628 patients achieved a response (response rate, 48%; 95% CI, 46.1%-49.9%), very similar to response rates of the 53.8% and 50.1% (range, 31.6%-70.4%) found in younger adult patients who were a mean age of 42.6 years.<sup>33,37,38</sup> The number needed to treat (NNT) for a response to antidepressants compared with placebo was 6.7 (95% CI, 4.8-10) for older adults, which was also comparable with that of younger cohorts that had an NNT of 6.1.<sup>33,38</sup>

Antidepressants are beneficial for older patients with depression, but the effects are modest. In one meta-analysis including 15 RCTs and 4756 patients older than 55 years, antidepressants were not found to be effective in the subgroup of patients older than 65 years.<sup>32</sup> Another meta-regression of RCTs including 34 RCTs and 3690 patients 60 years or older, found that with increasing age, antidepressant efficacy decreased.<sup>34</sup> Antidepressants may be less effective in older patients because they have a greater burden of somatic disorders such as cardiovascular diseases, ischemic brain changes (manifested as white matter hyperintensities in magnetic resonance imaging) and because their physicians have a tendency to prescribe suboptimal doses of antidepressants.<sup>20,21,32</sup>

### Indications for Antidepressants

Indications for antidepressant treatment in older adults are the same as they are for younger adults.<sup>39</sup> Antidepressant medications should not routinely be used for the treatment of persistent depressive symptoms that do not fulfill criteria for a mood disorder or for mild depression. Antidepressant medications are indicated for the treatment of more severe depression (eg, PHQ-9 score,  $\geq 10$ ). Mild to moderate depression in older patients may better be treated with psychotherapy, which may even be effective in more severe depression.<sup>40</sup>

Older patients usually have a greater burden of medical illnesses than younger adults. Their management may be compli-

cated by contraindications for antidepressants; for example, recent myocardial infarction, glaucoma, or hepatic or renal impairment. The presence of medical comorbid conditions may lead to inadequate antidepressant treatment response and poor tolerability of the medications.<sup>23</sup> The treatment of multiple diseases with many medications results in a greater risk of drug-drug interactions and adverse effects.

The most important classes of antidepressants are the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors. A summary of an example of the agents in these classes is presented in Table 2. Selective serotonin reuptake inhibitors are the most prescribed class of antidepressants and are advised as first-line treatment for older and younger adult patients.<sup>16,41</sup> Selective serotonin reuptake inhibitors have almost completely replaced the tricyclic antidepressants as first-line agents for treating depression because they are equally effective for treating depression, have fewer adverse cardiac effects, typically require a 1- to 2-dose escalation steps to achieve the defined daily dose, are more tolerable, have minimal anticholinergic effects, and have a low likelihood of resulting in a fatal overdose. Selective serotonin reuptake inhibitors have more interactions with other medications, which may be important for older patients with polypharmacy. Selective serotonin reuptake inhibitors may be associated with falls and osteoporosis. The majority of older adults need the same dose as younger adults, with only very old patients or patients with physical comorbidity needing dosages lower than the defined daily dose.

The discontinuation rate of antidepressants because of severe adverse events, such as sexual or cardiac dysfunction, is no different between younger and older adults, suggesting that these events occur at the same rate in younger and older patients.<sup>32</sup> However, data are limited about medication discontinuation in older patients compared with younger adults within the same study.

### Antidepressant Mechanisms of Action

How antidepressants work remains controversial. The monoamine hypothesis states that depression is due to an imbalance or deficiency of the monoamine neurotransmitters serotonin, norepinephrine, and dopamine.<sup>42</sup> Almost all antidepressant medications base their efficacy on this hypothesis. Pharmacologically, they do this by inhibiting serotonin and norepinephrine reuptake. It is not known if reuptake inhibition is responsible for the efficacy of antidepressants or is just a secondary phenomenon with no causal relation with efficacy. Alternative explanations of mechanism of action include the glutamate, neurogenic, epigenetic, and cortisol hypersecretion.<sup>43-45</sup> There is also an inflammatory hypothesis stating that inflammatory cytokines in the brain may play an important role in depression and that antidepressants' efficacy may be related to their specific anti-inflammatory effects.<sup>46</sup>

### Treatment-Resistant Depression

Remission is achieved in about one-third of all older patients who are treated with an antidepressant.<sup>33</sup> This means that two-thirds of these patients need additional treatment. Many treatment options are available, including titrating the antidepressant to full adult doses and switching to another class of antidepressants.<sup>24</sup> Nonpharmacological treatments (discussed below) should also be considered and can be combined with antidepressants. There is little evidence

Table 1. Selection of Meta-analyses of Antidepressant Treatment Studies in Older Patients With Depression

Source	No. of RCTs Included and Blinding	Systematic Review	Age Limit, y	No. of Patients	Drug Class <sup>a</sup>	Primary Outcome
Mittmann et al, <sup>26</sup> 1997	16 Double-blind	Not stated	≥60	NA	TCA, SSRI, MAOI, atypical antidepressant	No differences in response rates between 4 antidepressant classes (RR: TCA, 63.1%; SSRI, 57.7%; atypical drug, 33.4%; MAOI, not available), except SSRIs (RR, 57.7%) had a higher response rate than atypical antidepressants (RR, 33.4%)
Wilson et al, <sup>27</sup> 2001	17	Yes	55/60 <sup>c</sup>	1326	TCA, SSRI, MAOI	Treatment vs placebo Not recovering with TCAs: OR, 0.32 (95% CI, 0.21-0.47); NNT, 3.97 (95% CI, 3.88-4.05) SSRIs: OR, 0.51 (95% CI, 0.36-0.72); NNT, 8.45 (95% CI, 8.38-8.53) MAOIs: OR, 0.17 (95% CI, 0.07-0.39); NNT, 3.14 (95% CI, 2.99-3.29)
Taylor and Doraiswamy, <sup>28</sup> 2004	18	Yes	≥55	2252	TCA, SSRI, others	71.5% Of trials reported greater efficacy with drug than placebo. NNT for response for HDRS was 5 (95% CI, 3-9) for TCA; 8 (95% CI, 5-11) for SSRIs, 8 (95% CI, 5-11) for all antidepressants
Mottram et al, <sup>29</sup> 2006	32	Yes	≥55	NA	TCA, SSRI, MAOI, atypical antidepressant	No differences in efficacy between classes of antidepressants TCAs vs SSRIs had > withdrawal rates RR, 1.23 (95% CI, 1.05-1.43) for any reason; RR, 1.36 (95% CI, 1.09-1.70) for adverse events TCAs vs MAOIs had > withdrawal rates; RR, 2.27 (95% CI, 0.44-11.81) for adverse events
Nelson et al, <sup>30</sup> 2008	10 Double-blind	Yes	≥60	4165	Second generation	Antidepressants vs placebo OR for response, 1.40 (95% CI, 1.24-1.57), OR for remission, 1.27 (95% CI, 1.12 to 1.44) Mean pooled response rates for antidepressants was 44.7%, for placebo, 34.7%
Sneed et al, <sup>31</sup> 2008	16	Not stated	≥60	NA	TCA, SSRI, MAOI, others	Response rates, 46% (95% CI, 38%-54%) in placebo-controlled trials vs 60% (95% CI, 53%-67%) in comparator trials
Tedeschini et al, <sup>32</sup> 2011	15 Double-blind	Not stated	≥55	15 816 Younger adults; 4756 older adults	No classes used	Response rates for antidepressants vs placebo Higher for ≥55 y; RR, 1.304 (95% CI, 1.150-1.479) No difference: 65 or 75 y; RR, 1.128 (95% CI, 0.929-1.369) The RR of discontinuing antidepressants vs placebo due to adverse effects is no different (95% CI, 0.041 to 0.092; P = .29) when comparing younger adult with late-life major depression
Kok et al, <sup>33</sup> 2012	51 Double-blind	Yes	≥55	NA	TCA, SSRI, other	All 3 classes of antidepressant were more effective than placebo to achieve a response All antidepressants pooled together were more effective in achieving remission, but the 3 different classes of antidepressant were not more effective than placebo No differences were found in remission or response rates between classes of antidepressants Response rate, 48.0% for antidepressant vs 38.6% for placebo Remission rate, 33.7% for antidepressant vs 27.2% for placebo
Calati et al, <sup>34</sup> 2013	34 Double or single blind	Not stated	>60	3690	No classes used	A lower response rate in men, older age, and with a longer duration of the current episode (P<.001) A higher response rate in patients with a higher baseline severity and their first episode of illness (P<.001)
Nelson et al, <sup>35</sup> 2013	7 Double-blind	Yes	≥60	2283	Second generation	In this patient-level meta-analysis, only drug-placebo differences in response rates was robust (NNT, 4) in patients with an illness duration of >10 y and an HDRS score ≥21; age was not associated with response
Thorlund et al, <sup>36</sup> 2015	15	Yes	≥60	588	SSRI, SNRI	A network meta-analysis of SSRIs and SNRIs, suggesting that response for sertraline, paroxetine, and duloxetine was better than placebo; remaining interventions did not separate from placebo

Abbreviations: HDRS, Hamilton Depression Rating Scale; NNT, number needed to treat; OR, odds ratio; RCT, randomized clinical trial; RR, response rate; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

<sup>a</sup> Grouping of classes is not consistent across reviews.

Table 2. Classes of Antidepressants

Class	Common Adverse Effects	Specific Recommendations
SSRI		
(Es-)citalopram Paroxetine Sertraline	For all SSRIs: nausea, vomiting, dyspepsia, diarrhea, headache, sexual dysfunction	In general: no dose reduction in the older (compared to younger adults). In many guidelines first line of treatment, even in frail older.
SNRI		
(Des-)venlafaxine Duloxetine	Nausea, dizziness, dry mouth, headache Nausea, dry mouth, sleepiness, headache	In general: no dose reduction for older patients (compared with younger adults)
TCA		
Amitriptyline Desimipramine Nortriptyline	For all TCAs: sedation, dry mouth, constipation, postural hypotension, tachycardia/arrhythmia	In general: start at lower dose, then increase dose (sometimes at adult levels) and check blood levels to achieve therapeutic exposure
MAOI		
Phenelzine Moclobemide Tranylcypromine	Postural hypotension, sleep disturbances Sleep disturbances, dizziness, headache, nausea Postural hypotension, sleep disturbances	In general: limited evidence base in the older Dietary restriction may limit the use of phenelzine and tranylcypromine
Other		
Agomelatine Bupropion Mirtazapine Vortioxetine	Anxiety, headache, dizziness, sleepiness Sleepiness, headache, dizziness, tremor Increased appetite, weight gain, somnolence Nausea, loss of appetite, abnormal dreaming	In general: no dose reduction in the older (compared with younger adults)

Abbreviations: MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

to support the use of combinations of different antidepressants for treatment-resistant depression. Lithium augmentation is the only treatment that has good evidence for effectively treating older patients, with an overall response rate of 42% (95% CI, 21%-65%). Most studies define a decrease of 50% or more on a depression rating scale as a response.<sup>47</sup> A recent high-quality RCT that included 181 patients with a mean age of 66 years found that adding an atypical antipsychotic (aripiprazole) to an antidepressant (venlafaxine) resulted in 44% remission rate compared with 29% with the addition of placebo in patients resistant to treatment (NNT, 6.6; 95% CI, 3.5-81.8).<sup>48</sup> Electroconvulsive therapy is highly effective for patients not responding to other treatments and for other patient categories discussed below.<sup>16,24,41</sup>

### Depression Treatment in Frail Geriatric Patients and Those With Comorbid Conditions

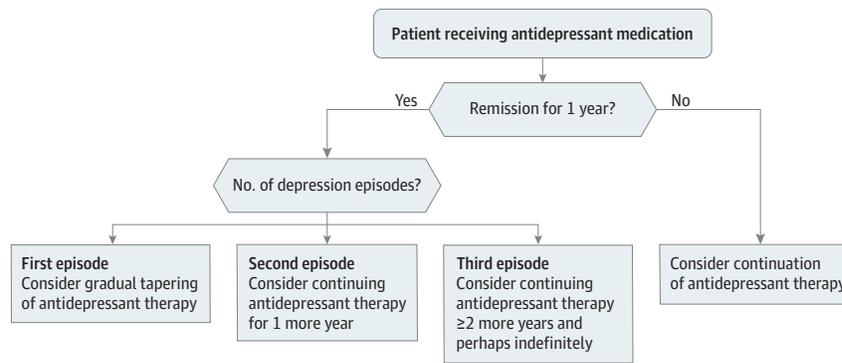
Frailty is a clinical state in which there is an increased vulnerability for developing increased dependency or increased risk of mortality when exposed to a stressor.<sup>49,50</sup> Frailty may be mistaken for major depression, resulting in patients being prescribed antidepressants inappropriately.<sup>51</sup> There is substantial overlap of both syndromes, and it is uncertain whether frailty is a comorbidity, cause, or consequence of depression.<sup>52</sup> A 4-year prospective study found that frailty predicted the onset of depression among participants who did not have depressive symptoms at baseline.<sup>53</sup> Adverse events or interactions of antidepressants with other medical treatments may be particularly severe in frail patients.<sup>54</sup> Exercise and protein-calorie and vitamin D supplementation may be beneficial for frail patients, but it is not known if these interventions benefit frail patients who also have depression.<sup>50</sup>

Most RCTs exclude older patients who have serious or unstable medical comorbidities, resulting in limited evidence to guide treatment for these patient groups. Nevertheless, antidepressant treatments can be effective for older patients with depression and concomitant, severe comorbid diseases.<sup>55</sup> Even patients in nursing homes may have a modest response to antidepressant medications.<sup>56</sup> Depression in older patients is often complicated by cognitive impairment, but when cognitive impairment results from depression, it can be partially or completely improved with depression treatment. Depression may be a risk factor for, a consequence of, or a concomitant comorbidity for dementia as well as an early sign of dementia preceding cognitive decline.<sup>57</sup> Antidepressants may not be effective when dementia is present.<sup>58,59</sup> Patients having both dementia and depression should have their symptoms monitored and not be given antidepressants as first treatment. They may benefit from psychosocial interventions such as behavioral therapy, music therapy, or caregiver education.<sup>60</sup>

### Antidepressant Maintenance Treatment

Once remission is achieved, it is not known how long antidepressant therapy should continue, for there are only a few studies that investigated this clinical problem. A recent meta-analysis of 8 RCTs<sup>61-63</sup> found that the risk of relapse or recurrence of depression among 925 patients was reduced by 28% (95% CI, 21%-36%) when interpersonal therapy, antidepressants, or the combination of these was compared with placebo. Therapy for these studies ranged from 6 to 36 months after remission. Antidepressants resulted in a NNT to avoid relapse of 3.6 (95% CI, 2.8-4.8) if antidepressant therapy was continued following remission. The efficacy and tolerability of long-term treatment with tricyclic antidepressants and SSRIs were

Figure. Suggested Algorithm for the Management of Antidepressant Maintenance Therapy



the same. A US Food and Drug Administration review of 15 antidepressant maintenance trials confirmed that these treatment results were similar to the treatment results among younger adults (mean age, 44 years).<sup>54</sup> Relapse rates when antidepressants were continued were 18.4% (95% CI, 13.2%-23.7%) vs 36.2% (95% CI, 30.2%-42.1%) when they were discontinued. Another review antidepressant maintenance therapy among older adults included antidepressants (6 RCTs) and psychological therapies (2 RCTs) and demonstrated less favorable results in 803 participants.<sup>64</sup> When antidepressant maintenance therapy was compared with placebo, no significant difference was found in recurrence rates at 6, 24, and 36 months. The only statistically significant effect of antidepressants was found at 12 months (3 RCTs, relative risk of recurrence, 0.67; 95% CI, 0.55-0.82). The lack of effect of antidepressants in this study may be explained by inadequate sample size for subgroup analyses.

Based on the available data, it is not possible to make definite recommendation about when to stop maintenance treatment. Expert consensus guidelines recommend that discontinuation of antidepressants be considered a year after remission is achieved in depressed, older patients who have had a single episode of depression. Patients who have had 2 episodes of depression should probably continue antidepressant therapy for 2 years. If the patient has had 3 or more episodes of depression, he/she should have at least 3 years of antidepressant therapy or could possibly receive it indefinitely (Figure).<sup>41</sup> Other factors influencing the decision to continue antidepressant therapy include patient preferences, severity of the last episode, number of treatments needed to achieve remission, number of years between episodes of depression, number and severity of adverse effects from the medication, and presence of risk factors for depression such as chronicity, disability related to medical multimorbidity, and lack of social support.

## Other Treatments

Depression-specific psychotherapy is recommended as an initial treatment choice for patients with mild to moderate depression.<sup>15</sup> The overall effect size of psychotherapy (such as problem solving therapy, cognitive behavioral therapy, and interpersonal psychotherapy) among older patients, compared with control groups, is 0.64 (Hedges *g*, 95% CI, 0.47-0.80) with a NNT of 3.<sup>40,65,66</sup> Psychotherapy is comparable with the effectiveness of antidepressants.

Cognitive behavioral therapy is the best studied psychotherapeutic intervention. A number of meta-analyses found large pooled effect sizes, ranging from 0.70 to 1.34, in favor of cognitive behavioral therapy over controls.<sup>67,68</sup> However, it is not clear whether very old patients (>75 years) or frail older patients were included in these studies. Thus, the influence of physical diseases, frailty, and cognitive impairment on the efficacy or feasibility of psychotherapy has not been assessed in high-quality studies. However, especially for these patients, tolerance of antidepressants may be poor, so psychotherapy may be an effective alternative.

Electroconvulsive therapy is the most effective treatment for older patients with major depression, with efficacy ranging from 60% to 80%.<sup>16,24,69</sup> Electroconvulsive therapy is also indicated for patients with severe or psychotic depression and patients with severe malnutrition or a medical condition that worsens because they have refused to take their medication.<sup>16,24,70</sup>

Exercise offers a modest benefit compared with active usual care or nonactive control interventions including equal contact, attentional control, or being on a waiting list as long as the RCT lasts before receiving treatment.<sup>71,72</sup> Although high-quality clinical studies investigating the effect of exercise for treating depression among older patients are lacking, these systematic reviews of the available RCTs suggest that exercise may benefit older patients, including very old patients, if they are willing to participate actively in an exercise program.

## Polypharmacy or Stopping Antidepressants

The Screening Tool of Older Persons Prescriptions and Screening Tool to Alert clinicians to Right Treatment (STOPP/START) criteria is a valid and reliable screening tool that enables physicians to avoid potentially inappropriate medications, undertreatment, or errors of prescribing omission.<sup>73-75</sup> For example, because tricyclic antidepressants are more likely to cause an adverse reaction than are SSRIs or serotonin-norepinephrine reuptake inhibitors, their initiation as a first-line treatment is not considered appropriate. Use of the STOPP/START criteria may help prevent polypharmacy, usually defined as using 5 or more medications. Polypharmacy is associated with falls, adverse drug events, hospitalization, mortality, functional limitations and cognitive dysfunction.<sup>76</sup> Implementing the START/STOPP criteria among, for example, patients in nursing homes, who often

use more than 10 different medications, reduced the number of medications, falls, and costs of care.<sup>77</sup>

Particular attention should be given to the start of antidepressant medications when polypharmacy is present.

Medications that are associated with depression as a potential adverse effect, include corticosteroids, angiotensin-converting enzyme inhibitors, and lipid-lowering drugs, although the data on many drugs are contradictory.<sup>78</sup> If possible, these drugs should be stopped in a patient with depression. Many patients with depression are prescribed benzodiazepines, often because the depression diagnoses is missed and benzodiazepines are used to treat the insomnia or anxiety that are prevalent symptoms of a depression. Benzodiazepines are not effective in the treatment of depression and are associated with falls, sedation, and cognitive impairment.<sup>79</sup> According to a meta-analysis including 10 studies involving younger adults, stopping benzodiazepines resulted in a mean improvement of cognitive function after 3 months with an effect size of 0.41 (SD, 0.22).<sup>80</sup>

It is not known how to best stop use of antidepressant medications. Discontinuation symptoms may occur when stopping or reducing the dose of antidepressant medications. This results in a variety of physical and emotional symptoms such as a flu-like syndrome, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal. Because the symptoms of antidepressant discontinuation include changes in mood, sleep, and appetite, they are sometimes mistaken for signs of a relapse into depression. Discontinuation symptoms are usually mild and self-limited, typically last about a week, but can be severe, particularly if the drug is stopped abruptly.<sup>81</sup> A gradual reduction of antidepressant medication dose over a 4-week period is advised, although some patients may require a longer time to discontinue these medications. This is particularly true for drugs such as paroxetine and venlafaxine because of their short half-life.<sup>15,81</sup> After antidepressant medications are discontinued, patients should

be monitored for several months and have the medications started again if depression symptoms recur.<sup>15</sup>

A systematic review of medication withdrawal in older patients identified only 1 double-blind RCT and 1 open-label RCT of antidepressant (SSRIs) withdrawal.<sup>82</sup> Both studies involved patients with dementia in nursing homes, limiting the generalizability of the results for patients who do not have dementia. However, in both studies, withdrawal was not associated with major withdrawal syndromes and was successful in most cases.<sup>83,84</sup> Predictors of success were low to moderate depression severity prior to the withdrawal, early or no dementia, and age of 85 years or younger.<sup>84</sup>

## Conclusions

There is a large robust evidence base to support various treatments for depression in older adults. Treatment outcomes for older patients are generally similar to those observed for younger populations. This may not be true, however, for frail, very old patients with multiple medical comorbidities. Psychotherapy or exercise therapy may help treat depression in frail patients but the evidence for this is limited. Antidepressant medications can be very useful for treating depression in older patients but once these patients have responded, it is not clear how long older patients should continue taking these medications. In general, pharmacotherapy should be maintained at least 2 years for patients with a lifetime history of depression to avoid the risk of recurrence and chronicity. Older patients tend to have polypharmacy, complicating antidepressant therapy both because of the potential for drug-drug interactions and because the addition of another drug increases the complexity of pharmacy management in patients who may have limited cognitive abilities.

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**Study concept and design:** Kok

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**Drafting of the manuscript:** Kok, Reynolds.

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