Pharmacologic treatment of depression in the elderly

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Abstract

Objective To discuss pharmacologic treatment of depression in the elderly, including choice of antidepressants, titration of dose, monitoring of response and side effects, and treatment of unresponsive cases.

Sources of information The 2006 Canadian Coalition for Seniors' Mental Health guideline on the assessment and treatment of depression was used as a primary source. To identify articles published since the guideline, MEDLINE was searched from 2007 to 2012 using the terms *depression, treatment, drug therapy,* and *elderly*.

Main message The goal of treatment should be remission of symptoms. Improvement of symptoms can be monitored by identifying patient goals or by use of a clinical tool such as the Patient Health Questionnaire–9. Treatment should be considered in 3 phases: an acute treatment phase to achieve remission of symptoms, a continuation phase to prevent recurrence of the same episode of illness (relapse), and a maintenance (prophylaxis) phase to prevent future episodes (recurrence). Initial dosing should be half of the usual adult starting dose and be titrated regularly until the patient responds, until the maximum dose is reached, or until side effects limit further increases. Common side effects of medications include falls, nausea, dizziness, headaches, and, less commonly, hyponatremia and QT interval changes. Strategies for switching or augmenting antidepressants are discussed. Older patients should be treated for at least a year from when clinical improvement is noted, and those with recurrent depression or severe symptoms should continue treatment indefinitely. Treatment of specific situations such as severe depression or depression with psychosis is discussed, including the use of electroconvulsive therapy. Criteria for referral to geriatric psychiatry are provided; however, many family physicians do not have easy access to this resource or to other nonpharmacologic clinical strategies.

Conclusion The effectiveness of pharmacologic treatment of depression is not substantially affected by age. Identification of depression, choice of appropriate treatment, titration of medications, monitoring of side effects, and adequate duration of treatment will improve outcomes for older patients.

EDITOR'S KEY POINTS

- Major depression affects up to 20% of people older than 65 years of age. Assessment and management of depression is challenging in older patients, especially those who are frail and those with comorbidities.
- Elderly patients with depression should be informed of their diagnosis, as many older patients taking antidepressants are unaware of their diagnosis of depression, and increasing patient and family understanding might affect outcomes by improving treatment adherence.
- Many older patients with depression have substantial comorbidities, and optimization of medical conditions and selection of antidepressants with regard to minimizing drug interactions is important. Concurrent psychiatric disorders can also affect outcomes. Factors to guide antidepressant choice can include previous response, concurrent conditions, type of depression, other medications, and risk of overdose.

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Case

Mr C. is an 85-year-old man with complaints of fatigue, decreased appetite, and a 2.5-kg weight loss over the past 6 months. He also reports changes in his short-term memory. His medical history is relevant only for cardiovascular disease, and he currently takes an angiotension-converting enzyme inhibitor and a statin.

*You administer a Montreal Cognitive Assessment[1] to assess his cognition and he performs well, scoring 26 out of 30. You conduct a full history and physical examination and no underlying physical illness is identified. You wonder whether Mr C. might be suffering from major depression. You apply the SIG E CAPS mnemonic (**Table 1**)[1] to screen for symptoms.*

He has had a change in sleep habits lately and reports considerable worry that his symptoms might be a sign of underlying cancer. He used to be active with his local Rotary Club and walked 3 km daily with a seniors group, but now spends much of his time resting on the couch. He no longer enjoys the weekly visits from his grandchildren. He denies suicidal thoughts or thoughts of self-harm.

Major depression affects up to 15% to 20% of people older than 65 years of age.[1] It has serious consequences for health, including decreased function, poor nutritional intake, and increased risk of death by suicide. The diagnosis of depression is difficult, particularly in the presence of frailty and comorbidities. In the elderly the presentation of depression might be variable and atypical (**Table 1**).[1,2]

Optimal outcomes might also be challenging to obtain with frail older patients. Although medications are only part of the treatment of depression, this article will focus on pharmacologic treatment, including choice of antidepressants, titration of dose, and treatment of unresponsive cases.

Sources of information

The 2006 Canadian Coalition for Seniors' Mental Health (CCSMH) guideline on the assessment and treatment of depression[1] was used as a primary source. In order to identify English-language research articles published since the guideline was developed, MEDLINE was searched from 2007 to 2012 using the terms *depression, treatment, drug therapy,* and *elderly*. Articles cited in papers were also reviewed and referenced when appropriate.

Main message

Initiation of therapy. Mr C. appears to have a unipolar major depressive episode without psychotic features. Sharing the diagnosis is an important first step. Evidence suggests many older patients taking antidepressants are unaware of their diagnosis of depression,[3,4] and increasing patient and family understanding might affect outcomes by improving treatment adherence. Sharing the diagnosis also provides the opportunity to identify treatment goals for the individual patient, which can be important for gauging response and titrating medication dose. For example, anxiety is a common manifestation of depression in older people and can be set as a possible target symptom.

The goal of treatment has traditionally been improvement in symptoms using a validated scale (eg, 50% reduction on the Hamilton Depression Rating Scale or the Patient Health Questionnaire–9).[5] However, the ideal goal should be remission of symptoms.[6] Choosing a more aggressive target is less likely to lead to undertreatment or "therapeutic nihilism" that might be more common when treating older patients.[7] Monitoring response using a self-administered clinical tool such as the Patient Health Questionnaire–9 might be helpful.

> *Given Mr C.'s presentation, antidepressant medication or psychotherapy or a combination of both is recommended (strength of CCSMH recommendation A; A recommendations are directly based on evidence from meta-analysis of randomized controlled trials or at least 1 randomized controlled trial). In most centres in Canada, access to psychology or psychotherapy services is limited (unless the family physician can provide it), given the low likelihood of third-party insurance among elderly patients to support privately paid care.*

Treatment should be considered in 3 phases:

- an acute treatment phase to achieve remission of symptoms;

Table 1. Presentation of depression in the elderly: X *indicates the symptom is prominent;* XX *indicates the symptom is very prominent.*

TYPICAL SYMPTOMS	PROMINENT IN ELDERLY PATIENTS	PROMINENT IN YOUNGER PATIENTS
SIG E CAPS		
• Sleep (insomnia or excess sleep)	XX	X
• Interest (anhedonia)	X	X
• Guilt	X (often feeling a burden to family)	XX
• Energy	XX	X
• Concentration	X	X
• Affect (dysphoria)		XX
• Psychomotor changes	XX	X
• Suicide	X (higher rate, especially for older men)	X
Other		
• Anxiety	XX	X
• Decreased appetite or weight loss	X	X
• Complaints of memory loss	XX	
• Pain	X	
• Fatigue	XX	X

Data from the Canadian Coalition for Seniors' Mental Health.[1]

- a continuation phase to prevent recurrence of the same episode of illness (relapse); and
- a maintenance (prophylaxis) phase to prevent future episodes (recurrence).[8]

Regardless of the therapy chosen, it is important to consider the social and environmental context of each patient.[9] There is evidence that improved socialization and supportive approaches including life review,[10] music therapy, and exercise[11] can prevent and improve depression (A recommendation). Psychotherapies recommended for geriatric depression include behaviour therapy, cognitive-behavioural therapy, problem-solving therapy, brief dynamic therapy, interpersonal therapy, and reminiscence therapy (A recommendation).

Mr C. reluctantly concedes that you might be right with the diagnosis and consents to starting an antidepressant. You work with him to identify treatment goals: improved sleep, return to Rotary Club activities, and being able to get back to his walking. His most important goal is to begin enjoying his grandchildren again.

Pharmacologic treatment. Many older patients with depression have substantial comorbidities such as heart failure, diabetes, and cancer; chronic disease is a risk factor for development of depression. Optimization of medical conditions and selection of antidepressants with regard to minimizing drug interactions is relevant to depression management. Concurrent psychiatric disorders such as anxiety and dementia can have an effect on outcomes, but antidepressants appear to have similar effectiveness in elderly and younger patients.[12,13] Although the presence of medical illness can make the diagnosis of depression more difficult, there is no clear evidence that comorbid conditions substantially decrease the effectiveness of antidepressants.[14]

Treatment of depression in patients with dementia can be challenging. Recent evidence suggests that there is lower efficacy for antidepressants in patients with dementia.[15,16] Cholinesterase inhibitors should be considered in the treatment of depressive symptoms such as apathy and decreased initiative, as antidepressants might not be helpful for these symptoms.[17]

Factors to guide antidepressant choice (**Table 2**) can include previous response, concurrent conditions (eg, avoiding anticholinergic agents in men with benign prostatic hypertrophy), type of depression (eg, bipolar versus unipolar, presence of psychotic features), other medications, and risk of overdose.[1,18] There is some evidence that choices can also be guided by concurrent symptoms (eg, nortriptyline or duloxetine for concurrent pain[19] and mirtazapine with anxiety[20]).

Psychostimulants are not well studied in the elderly and have the potential to contribute to agitation and insomnia. A Cochrane review found small benefits in small studies.[21]

Benzodiazepines have, at best, a very limited short-term role in handling anxiety and insomnia symptoms until safer and more comprehensive antidepressants start working.

Side effects. Side effects are common; up to 12% of participants in studies drop out because of side effects.[22,23] Antidepressants share similar side-effect profiles; nausea, constipation or diarrhea, dizziness, headache, insomnia or somnolence, and sexual dysfunction are commonly reported.[24] Patients who switch agents commonly report similar side effects with the replacement agent.[24] Although tricyclic antidepressants (TCAs), particularly amitriptyline, anecdotally have considerable effects on cognition and cardiac conduction abnormalities, they are as well tolerated as newer agents in studies.[22] If TCAs are used, nortriptyline and desipramine have the lowest anticholinergic burden. Attention to other medications is crucial in avoiding adverse drug reactions and interactions.[23]

Increased risk of falls is a well recognized side effect of antidepressants, including the newer agents.[25] Patients at high risk of falls should undergo a falls assessment to mitigate this risk before receiving antidepressants.

Approximately 8% of people starting selective serotonin reuptake inhibitors (SSRIs) or venlafaxine will develop hyponatremia related to syndrome of inappropriate secretion of antidiuretic hormone. This is reversible but should be monitored by checking blood levels at about 1 month after starting (C recommendation; C recommendations are directly based on evidence from nonexperimental descriptive studies or are extrapolated from more rigorous studies). A 2009 systematic review did not find an association between SSRI use and suicide in older patients.[26] However, the elderly are at higher risk of suicide overall, and identification of suicide risk at the time of assessment and during follow-up is important.[26]

In May of 2012, Health Canada issued a warning of caution related to higher doses of citalopram and escitalopram, citing concerns about prolongation of QT interval.[27] Official guidelines have not arisen from this recommendation, but caution should be exercised when prescribing doses greater than 20 mg of citalopram and 10 mg of escitalopram in patients older than 65 years of age, and attention should be paid to concurrent prescribing of other agents that can affect QT interval. A baseline electrocardiogram (ECG) can help to inform this decision, and follow-up ECG can be considered if treatment is started in patients with QT intervals in the high-normal range or if medications with risk of interaction are started.

Titration and monitoring. The CCSMH guidelines recommend starting with half of the "usual" starting

Table 2. Antidepressant choices for older patients

GENERIC NAME	TRADE NAME	STARTING DOSE, MG/D	AVERAGE DOSE, MG/D	MAXIMUM RECOMMENDED DOSE, MG/D	COMMENTS AND CAUTIONS
SSRI					
• Citalopram	Celexa	10	20–40	20 for those older than 65 y 40 for others	QTc prolongation
• Escitalopram	Cipralex	5	10–20	10 for those older than 65 y 20 for others	QTc prolongation
• Sertraline	Zoloft	25	50–150	200	Like all SSRIs, risk of nausea, SIADH
SNRI					
• Venlafaxine	Effexor	37.5	75–225	375*	Might increase blood pressure
Other					
• Bupropion	Wellbutrin	100	100, twice daily	150, twice daily	Might cause seizures
• Mirtazapine	Remeron	15	30–45	45	Might cause sedation, especially at lower doses
Tricyclic					
• Desipramine	Norpramin	10–25	50–150	300	Anticholinergic properties; cardiovascular side effects; monitor blood levels
• Nortriptyline	Aventyl	10–25	40–100	200	Anticholinergic properties; cardiovascular side effects; monitor blood levels

SIADH—syndrome of inappropriate secretion of antidiuretic hormone, SNRI—serotonin noradrenergic reuptake inhibitor, SSRI—selective serotonin reuptake inhibitor.
*For severe depression.
Modified from the Canadian Coalition for Seniors' Mental Health with permission.[1]

dose cited in the *Compendium of Pharmaceuticals and Specialties*,[28] with a scheduled titration based on tolerance and response. It is advisable to develop a plan for titration at the time of initiation and to review patient and physician goals that will indicate response. Without such a schedule, patients might take longer to reach therapeutic doses and endure a longer period of symptoms.[29] It is recommended that doses be increased regularly until the maximum cited dose is reached, side effects limit further increases, or good symptom improvement occurs. The geriatric adage "start low and go slow" should be modified to "start low and go slow, but go!"

Mr C. starts taking 10 mg of citalopram and experiences mild nausea and some increase in anxiety. After 10 days his dose is increased to 20 mg, which is tolerated. After 2 weeks he reports a small improvement in sleep and anxiety. He has gone with the walking group a few times but is still spending much of the time in his house. After 1 month of treatment his serum sodium level is checked to rule out syndrome of inappropriate secretion of antidiuretic hormone and the results are found to be normal. An ECG shows no change in QTc (<450 milliseconds), and the dose is increased to 30 mg with no ECG change. After 4 weeks at this dose you review his target symptoms.

If titration leads to the maximum dose, it is important that patients receive an adequate duration of therapy at that dose. Checking adherence is important, as patients might not voluntarily report missing doses accidently or intentionally owing to side effects. Change in medication should be considered if patients have no response after 4 weeks on the maximum dose or have only partial response after 8 weeks of treatment (C recommendation). There is no clarity on the optimal approach to switching or augmenting treatment. If there has been no benefit, the agent can be switched to another drug in the same or in a different class. Although the risk of serotonin toxicity and side effects might increase with more than 1 agent, it is not usually necessary to discontinue an antidepressant completely before starting a new agent; usually one can start the new agent at the lowest dose of the initial medication. If fluoxetine is the initial antidepressant, a wash-out of several weeks will be needed given its long elimination half-life and potential for interaction.[30]

Augmentation usually involves addition of another antidepressant, lithium, or an atypical antipsychotic. Lithium is most advisable in patients with possible bipolar disease and should be avoided with patients in multiple medical issues and risk of drug interactions.

There remains little evidence to support augmenting with antipsychotics in the very elderly who have higher risks of adverse events including extrapyramidal symptoms.[31-33] Family physicians without experience in augmentation should consider referral to geriatric psychiatry.

Approximately 10% to 20% of patients develop chronic depressive symptoms despite treatment and 25% to 30% of patients fail to respond to initial therapy. Risk factors for poor response include comorbid dementia, substance abuse, and substantial physical disabilities.

Mr C. reports partial improvement in his symptoms; he is only doing his walk a few times a week. Visits with the grandchildren remain difficult and he is sleeping poorly. You decrease his citalopram to 20 mg and titrate off, overlapping with 37.5 mg venlafaxine. The dose of venlafaxine is increased every 2 weeks and at 150 mg daily he reports better sleep and improved interest and is much better with visits. He asks you how long he needs to continue taking the medication.

Continuation and maintenance treatment. There is some evidence for higher rates of relapse after discontinuation of treatment in older patients compared with younger people,[34] and it is recommended that the duration of treatment should be a minimum of 12 months starting from the time of remission (and up to 2 years) (B recommendation; B recommendations are directly based on evidence from non-randomized controlled trials or other quasi-experimental studies, or extrapolated from evidence from randomized controlled trials). In a systematic review of "continuing treatment phase" (duration of studies 24 weeks to 3 years), the number of patients needed to treat (NNT) for all antidepressants to prevent 1 additional relapse or recurrence was 3.6 (95% CI 2.8 to 4.8). Interestingly, the NNT for TCAs was 2.9 (95% CI 2.2 to 4.6), compared with an NNT for SSRIs of 4.2 (95% CI 3.2 to 5.9).[22]

If the decision is made to stop antidepressants, the dose should be reduced over several months with monitoring for relapse (D recommendation; D recommendations are based on expert opinion). Indefinite treatment should be considered for patients who have severe depression, have a history of recurrent depression, require electroconvulsive therapy (ECT), or have only partial resolution of symptoms (D recommendation).

Specific circumstances

Psychotic depression: The presence of psychosis should prompt referral to geriatric psychiatry when available, as the risk of morbidity and mortality becomes higher and management can be more difficult. Electroconvulsive therapy should be considered early in psychotic depression.[1] If pharmacologic treatment is used, antipsychotics and antidepressants in combination with ECT should be considered if treatment is not effective (D recommendation).[35]

Electroconvulsive therapy: Electroconvulsive therapy can also be a life-saving treatment in cases in which metabolic or nutritional derangement is severe or in which suicidal thoughts are not responding to other treatments. It should be considered in severe cases of depression and when other treatment strategies are ineffective. For some patients, ECT might be the only treatment that helps improve quality of life and decreases the health effects of depression (D recommendation).[36]

Criteria for referral: The criteria for psychiatric referral are outlined in **Box 1**.[1] Geriatric psychiatrists have specific expertise in the diagnosis and treatment of late-life depression, but many family physicians will not have access to geriatric psychiatry services. Patients in long-term care commonly have comorbidities and complexities that can make management difficult, but they often have limited access to psychiatric services. It is worth being aware of resources for depression in one's region, especially with the aging population and increasing complexity of patients.

Box 1. Criteria for referral

At the time of diagnosis, clinicians should refer patients with the following conditions to psychiatry services, if available:

- psychotic depression
- bipolar disorder
- depression with suicidal thoughts or intent

Patients with the following conditions might also benefit from such referral:

- depression with comorbid substance abuse
- major depressive episode or severe depression
- depression with comorbid dementia

Additionally, when physicians experience the following, referral might be warranted:

- uncertainty about management of partial or unresponsive depression
- inexperience with use of augmentation options and agents

Modified from the Canadian Coalition for Seniors' Mental Health with permission.[1]

After a year of remission, you discuss titration off the antidepressant with Mr C. He is sceptical, given concerns about relapse. At 18 months he feels he is taking too many medications and agrees to try stopping the venlafaxine. This is titrated down over 4 months without withdrawal symptoms, and 6 months later he reports no recurrence of symptoms.

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Competing interests
None declared

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