



## Depression in Older Adults - A Review

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### Abstract

The prevalence of major depressive disorder (MDD) is estimated to be 13.3%, while depressive symptoms are estimated to occur in 28.4% of older adults. A range of medical, functional, and psychosocial risk factors contribute to depression in this population. Depression in older adults may present differently than in younger adults with more physical complaints. Diagnosis becomes even more challenging in the presence of delirium and dementia, which often overlap in an older adult with MDD. It is important to assess suicide risks in older adults with depressive symptoms. Psychotherapy is recommended for mild to moderate depression, while antidepressants should be considered for severe depression or when psychotherapy is not available. Careful monitoring of side effects is important in older adults due to reduced physiological reserves.

### Introduction

Depression in older adults is often under-recognized and even less commonly treated. The World Health Organisation (WHO) estimates that the overall prevalence of depression in adults > 60 is 5.7%. Earlier studies reported the prevalence of major depressive disorder at any given time in community samples of adults aged >65 ranges from 1-5% in most large-scale epidemiological investigations in the United States and internationally, with the majority of studies reporting prevalence in the lower end of the range [1]. Recent systematic review and meta-analyses showed that the average prevalence of major depressive disorder in older adults is 13.3% (95% CI: 8.4-20.3%) [2], suggesting a possible increase in the prevalence over time. If preclinical depressive symptoms were included, the average prevalence of depressive symptoms or clinical depression in older adults can be as high as 28.4% [3].

Diagnosis and management of depression in older adults can be challenging for clinicians due to the atypical presentation of depression in this age group. Among the less experienced physicians, older adults presenting with depression were extensively worked up for medical causes, which further increased the anxiety and ruminations associated with poor health [4].

### Case Presentation

Mrs. A is a 72 year old lady who was admitted with changes in her behavior for 5 days prior to admission. She was community ambulant and the main caregiver for her disabled husband pre-morbidly. In the ward, she was agitated and aggressive towards all the care team and on occasions, she was in danger of causing herself and the other patients nearby serious physical harm by trying to abscond from the ward and was physically threatening anyone who tried to stop her. Physical examination was unremarkable except for full rectum on per rectal examination. Her blood investigations, chest radiograph and electrocardiogram (ECG) were all within normal limits. On further questioning, her domestic helper told us her best friend passed away about a month prior and she had worsening insomnia since. Mrs. A had longstanding insomnia for which she self-medicated with hydroxyzine. She consulted a few psychiatrists for worsening insomnia and was given a combination of Mirtazapine, Fluvoxamine, Lorazepam, Alprazolam and Zopiclone when her symptoms persisted. It was difficult to ascertain which combination she was taking prior to admission. She was extensively worked up with MRI brain, EEG, lumbar puncture which were unremarkable. She refused to eat and had to be supported with nasogastric feeding tube. She was restrained

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physically intermittently when she turned aggressive. She eventually recovered after 6 weeks' stay in the ward and needed 4 weeks of rehabilitation to regain her function. However, at review 6 months after her discharge, her MMSE was 20/30 and she was no longer able to drive or trade in stock market like she used to be able to.

## Method

The authors searched the latest literature on depression in older adults using PubMed and generated a review on the risk factors, presentation, diagnosis and management of depression in older adults.

## Results

### Risk factors

Depression in older adults is influenced by multiple risk factors. The authors categorized them into medical, functional, and psychosocial domains. Medical risk factors include chronic medical conditions (especially stroke, arthritis, angina, asthma, cardiovascular disease and diabetes) [5-7], polypharmacy [8], and certain medications such as hypnotics [9]. Visual impairment [10,11] is also an identified risk factor. The association between functional dependence and depression is unclear as evidence is inconsistent [12]. However, based on the local clinical experience, loss of independence may trigger depression in a previously independent older adult. Psychosocial risk factors encompass life stressors [13,14], such as loneliness [7], social isolation [15] and financial distress [16]. There is no conclusive evidence that female gender or being single or widowed increased risk of depression in older adults [12].

### Clinical presentation

Depression in older adults may present differently compared to the younger adults. Older adults may have less affective symptoms such as dysphoria and worthlessness. In contrast, the older adult has more physical complaints such as sleep disturbances, loss of appetite and weight [18]. They may also exhibit more hypochondriasis and psychosomatic symptoms [19]. Cognitive dysfunction such as executive dysfunction, reduced attention span, poor memory and concentration are commonly reported as well [20]. Depression in older adults is associated with increased suicide risks. Suicide ideation should be routinely screened for in this group of individuals as, most older adults who committed suicide visited doctors within months of their death [21]. Individuals with severe depression, a history of serious suicide attempts, and limited social support were at higher risk for suicidal thoughts [22].

### Screening and diagnosis

Self-rating scales like Patient Health-Questionnaire-9 (PHQ-9)[23] and Geriatric Depression Scale (GDS) [24] are useful clinical tools for screening and bedside assessment. Cornell depression scale can be used to screen for depression in persons with dementia [25].

Alternatively, the Diagnostic and Statistical Manual of the American Psychiatric Association DSM V criteria for major depressive disorder (MDD) is a validated and quick screening tool, which requires >5 symptoms for a two-week period, one of which must include either depressed mood and/or loss of interest/pleasure in all activities most of the day. These symptoms must cause clinically significant distress and not be attributable to physiological effects of substance abuse, medical comorbidities or be better explained by psychiatric disorders

like schizophrenia, schizoaffective disorder or other psychotic disorders.

However, the prevalence of depressive symptoms that do not meet the threshold of MDD is substantial among older adults, with most studies reporting rates in the range of 15% [26].

## Treatment

The general aim for treatment is to achieve symptomatic remission, promote functional recovery, prevent relapse and recurrence, to delay or prevent further consequences like worsening of coexisting medical comorbidities, cognitive impairment leading to dementia, and eventually death. Successful treatment of depression also reduces caregiver burden. Adjunctive management strategies include referrals to community or social support services and psychologists for cognitive and behavioral interventions.

### Psychotherapy

Referrals to psychologist may be considered for older adults with mild to moderate late-life depression and their preferred first-line option [27]. Among the types of psychotherapy with positive results include cognitive behavioral therapy (CBT), problem-solving therapy (PST), and interpersonal psychotherapy (IPT) [28]. CBT focuses on providing older adults with coping strategies to manage low mood, while interpersonal psychotherapy aims to address and resolve complex interpersonal relationships. Other types are Reminiscence therapy (RT) and Brief dynamic therapy (BDT). Meta-analysis has shown that psychotherapy is as effective as pharmacotherapy in improving depressive symptoms [29] and results in an improved quality of life [30].

Psychotherapies should be offered as the first-line therapy for older adults with mild to moderate depression [31] and also to older adults with cognitive impairment [32]. However, it is often not available or freely accessible to most, except in large centers.

### Antidepressants

Medications should be considered for older adults with moderate to severe depression or mild depression who have no access to psychotherapy. Medication selection and monitoring should be done carefully for older adults due to impaired renal function, polypharmacy, hence, potential drug-drug interactions. Summary of the various antidepressants commonly used for treatment of MDD is shown in Table 1.

There are several classes of antidepressants available, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), agents with other mechanisms of action such as mirtazapine and bupropion, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs).

Selective serotonin reuptake inhibitors (SSRIs) are usually the first line therapy for major depressive disorder in older adults due to their favourable side effect profiles. Common adverse effects of SSRIs include gastrointestinal disturbance (e.g. nausea or diarrhea), sexual dysfunction, insomnia, agitation, drowsiness and syndrome of inappropriate antidiuretic hormone (SIADH) [33]. In addition, SSRIs may also lead to QT prolongation and orthostatic hypotension [34]. SSRI has also been reported to cause heightened fall risk [35], probably due to a combination of its sedative effects and associated orthostatic hypotension, and less commonly movement disorders.

Serotonin–norepinephrine reuptake inhibitors (SNRIs) such as Venlafaxine or Duloxetine may have adverse effects such as nausea, dizziness, diaphoresis, increased blood pressure, headache and sexual dysfunction [36]. Both Duloxetine and Venlafaxine have indications for management of neuropathic pain [37], while duloxetine is also licensed for treatment of chronic pain due to fibromyalgia and musculoskeletal pain.

There is some evidence suggesting that SSRI and SNRI may be associated with increased risk of GI bleeding [37-39] through its effect on the platelet function [40] and gastric acid secretion [41], particularly in patients who take nonsteroidal anti-inflammatory drugs [42]. However, their effects on intracerebral bleeding is less clear [43].

Mirtazapine is a tetracyclic antidepressant which increases noradrenergic and serotonergic neurotransmission by blocking  $\alpha_2$ -adrenergic receptors centrally. Adverse effects include sedation, increase in appetite and weight gain, orthostatic hypotension and dyslipidemia [36]. Rarely, mirtazapine has been reported to cause severe but reversible neutropenia [44,45].

Vortioxetine is a serotonin modulator which does not cause QT prolongation. However, side effects reported include nausea, vomiting, dizziness, bad dreams [46] and rarely hyponatremia [47]. There is some evidence that vortioxetine may enhance cognitive performance in patients with MDD and impaired cognitive function [48].

Bupropion is an antidepressant which may cause insomnia and agitation, angle-closure glaucoma and seizures [49]. Its mechanism of action is not fully understood but it is also licensed for use in smoking cessation [50].

Despite their effectiveness in treating depression, tricyclic antidepressants (TCAs) are associated with multiple serious adverse effects. These include anticholinergic effects, orthostatic hypotension, sedation, seizure, and cardiac arrhythmia [51]. TCAs are generally not recommended as the first line therapy for MDD among the older adults according to the Beers Criteria [52], unless there are other concomitant indications for TCA such as neuropathic pain [53].

Monoamine Oxidase Inhibitors (MAOIs) increase dopaminergic, noradrenergic, and serotonergic neurotransmissions through blocking monoamine oxidase. They may cause sleep disturbances and postural hypotension and have food-drug and drug-drug interactions that can lead to life-threatening serotonin syndrome or hypertensive crisis [54]. Like TCA, MAOIs are not generally recommended as the first line treatment for MDD.

All the above antidepressants increase the risks of serotonin syndrome, although the risk is higher among those taking SNRI or MAOI [55] or co-prescriptions of the above with other culprit drugs which increases the risks further [56]. Serotonin syndrome is defined as the triad of altered mental status, neuromuscular hyperactivity, and autonomic excitation [57]. Hunter serotonin toxicity criteria [58] is a useful clinical tool to diagnose serotonin syndrome based on the presence or absence of clinical symptoms (diaphoresis, agitation, and fever) and signs (clonus, hypertonia, tremor).

Serotonin syndrome is a rare complication related to treatment of MDD. Nevertheless, the risk is higher among the older adults due to reduced renal clearance and polypharmacy which increases risks of drug-drug interactions. Management of serotonin syndrome is beyond the scope of this review.

### *Efficacy of anti-depressants and monitoring for response*

There is clear evidence that anti-depressants are effective in treating major depressive disorder. In a meta-analysis of randomized controlled trials of the effectiveness of antidepressants among older adults, the number needed to treat for a response to antidepressants compared with placebo was 6.7 (95% confidence interval, 4.8-10) [60]. In a systematic review and network meta-analysis that examined the comparative efficacy of different antidepressants for adults, agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine and vortioxetine were found to be more effective than other antidepressants. On the other hand, fluoxetine, fluvoxamine, reboxetine and trazodone were found to be the least efficacious drugs [61].

The evidence for using medications to treat depressive symptoms that do not meet the criteria for major depression or depressive symptoms associated with dementia is less clear [26]. In clinical settings where MDD cannot be ascertained, yet the older adults exhibit depressive mood which interfered with quality of life or rehabilitation, a trial of antidepressant is sometimes prescribed. There are also circumstances where older adults with moderate to severe dementia who are unable to cooperate with full assessment of mood disorders while presenting with agitation, aggression, insomnia [62] may have depression as the underlying cause. It is important to closely monitor for adverse effects of these medications among this group of vulnerable older adults as they would not be able to communicate the adverse effects they experience with the drugs. For frail older adults with poor reserves, it is safer to follow the general principle of “start low and go slow” when initiating medications for MDD. Routine recommendations include monitoring renal function, serum sodium levels and ECG to exclude prolonged QTc prior to starting treatment.

Older adults should be monitored for 4-6 weeks at the beginning of treatment to assess response to treatment. Dosage may be titrated based on their response. The PHQ-9 can be used as a tool for monitoring treatment response. If the older adult does not respond to medications despite optimal dosing, alternative anti-depressants may be considered. For older adults who are refractory to commonly used antidepressant therapy, novel treatments have been reported in the literature. Combination of antidepressants or use of adjuvants may be considered for resistant cases, bearing in mind the higher risks of drug interactions and serotonin syndrome [56]. Referral to a psychogeriatric specialist is appropriate at this stage.

### *Maintenance therapy for anti-depressants*

Previous systematic reviews [63,64] and a recent randomized clinical trial [65] have demonstrated that discontinuation of antidepressant therapy among patients who have responded to treatment is associated with a higher risk of relapse. However, there is still a lack of data on the optimal treatment time before attempting to trial off medication. According to expert opinion [66], discontinuation of antidepressants may be considered after one year of sustained response in patients with no history of relapse. In patients with a history of one relapse, discontinuation may be considered after two years of sustained response. In patients with two or more relapses, treatment should continue for at least three years or indefinitely. In cases where the decision is made to stop antidepressants, it is crucial to gradually taper off the medication, as sudden discontinuation may result in withdrawal symptoms such as dizziness, headache, nausea, and fatigue [67].

**Table 1. Antidepressants and their adverse effects**

Medication	Adverse effects	Remarks	References
<b>SSRI</b>			
(Es-)citalopram	Gastrointestinal: nausea/ diarrhea Sexual dysfunction Insomnia/agitation SIADH Drowsiness Weight gain QTc prolongation Orthostatic hypotension Increased fall risk	Activating	[33-35]
Paroxetine		Sedating, avoid in older adults (Beers Criteria)	
Fluvoxamine		Sedating	
Sertraline		Activating, diarrhea	
Fluoxetine		Activating, long half-life (70-80H)	
<b>SNRI</b>			
Venlafaxine	Nausea, dizziness, diaphoresis Increased BP Headache Sexual dysfunction	Licensed for chronic pain management[37]	[36]
Duloxetine			
<b>Other</b>			
Mirtazapine	Sedating, increased appetite, weight gain Orthostatic hypotension Dyslipidemia Potential for neutropenia		[36, 44, 45]
Vortioxetine	Nausea and vomiting Dizziness Bad dreams	Does not prolong QTc May enhance cognitive function in MDD patients with secondary cognitive impairment [48]	[46]
Bupropion	Insomnia/agitation Angle-closure glaucoma Seizure	Mechanism not fully understood Labeled for smoking cessation [50]	[49]
<b>TCA</b>			
Amitriptyline	Anticholinergic, cardio toxicity Orthostatic hypotension	Avoid in older adults due to cardio toxicity and anticholinergic properties	[51]
Nortriptyline	Anti-histaminic H1 effect[59] Lower seizure threshold		
Desipramine	Cardiac arrhythmia		
MAOI	Sleep disturbances Postural hypotension	Food-drug, drug-drug interaction leading to life-threatening adverse effects such as serotonin syndrome or hypertensive crisis Limited evidence in older adults	[54]

SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor; TCA: Tricyclic Antidepressant; MAOI: Monoamine Oxidase Inhibitor

**Other treatment modalities**

**Electroconvulsive therapy (ECT)**

ECT is recommended as the first-line treatment for older adults with major depressive disorder with life-threatening poor oral intake and are at serious risk of suicide. ECT is also recommended as the first-line treatment for those patients with delusional depression which are less responsive to standard medications. It is also highly effective in treatment for MDD and mania in older adults. Cognitive adverse effects like anterograde and retrograde amnesia are the most common drawback for treatment with ECT [68].

**Repetitive Transcranial Magnetic Stimulation (rTMS)**

rTMS is a noninvasive procedure that is typically used when the other treatment options for depression have failed. Two major modalities of rTMS used are high frequency rTMS (≥1 Hz) and low frequency rTMS (≤1 Hz), which have stimulating and inhibitory effects on the cerebral cortex, respectively [69]. It is postulated that patients with depression have asymmetrical functioning of the frontal lobe [70] and thus inhibitory (low frequency) stimulation has been applied to the right dorsolateral prefrontal cortex (DLPFC) [71]. Treatment regimen is usually delivered daily for 6 weeks or 30 treatments. Studies shows that response to rTMS in older adults is similar to younger adults but

may occur at a slower rate [72]. It is also regarded as safe, with low fall-out rates [73].

### *Ketamine*

Intranasal ketamine is a new FDA-approved treatment in 2019 for adults with treatment-resistant MDD. There have been studies conducted in adults with depression but only limited published studies in older adults [74]. It is recommended that this medication be administered only at treatment centers which offers multidisciplinary care to patients with treatment resistant depression.

### **Navigating the 3 D's - Depression, Dementia and Delirium**

Depression and delirium are clinical syndromes with overlapping symptoms and possibly shared underlying pathologies [75]. Delirium tends to have a more acute onset and fluctuating course compared to depression and has less complex psychotic symptoms [75]. A history of depression is associated with a higher risk of delirium [76,77], while incident delirium is associated with an increased risk of depression [76]. Distinguishing between the two can be challenging, especially in cases of hypoactive delirium. It is important to consider delirium as a differential diagnosis and ensure its resolution before diagnosing and treating depression.

Depression is associated with cognitive impairment that may mimic dementia [78], while depressed mood is common in patients with dementia. Comorbid depression occurs in 30% of Alzheimer's dementia cases [79] and doubles the risk of developing dementia in the older adult [79,80]. Differentiating between the two conditions can be difficult and requires longitudinal follow-up. However, a prior history of depression at a younger age, more rapid progression (weeks to months rather than years), and significant improvement in cognition with antidepressant treatment increase the likelihood of a diagnosis of depression [81].

### **Proposed Clinical Approach to Depression in Older Adults**

The presence of risk factors such as recent stroke, social isolation, low socioeconomic status, or recent life stressors should increase suspicion of depression in older adults. Depression should also be considered in patients presenting with non-specific somatic or constitutional symptoms without a clear medical explanation.

A targeted history from the patient and their family should be taken to elicit symptoms such as low mood, anhedonia, guilt, hopelessness, insomnia, appetite changes, or suicidal ideation. A standard screening questionnaire such as the GDS and PHQ-9 can be used to screen for depressive symptoms. The DSM-V criteria should be applied to confirm the diagnosis of major depression and differential diagnoses such as delirium, bipolar disorder or dementia should be excluded. All older adults who present with depressed symptoms should be screened for suicidal ideation and/or plans, since suicide risk is high among the older adults [21].

Treatment for depression in older adults may include antidepressants and psychotherapy according to patient preferences and comorbidities. Response to treatment can be monitored using changes in PHQ-9 score [82] and medication dosage may be adjusted or switched if needed. In patients who have responded well to medication for at least one year and have no risk factors for relapse, weaning off therapy may be considered. Patients with depression refractory to first line treatment should be referred to a psychogeriatric specialist for further management.

In the case presented at the beginning of this article, the patient was admitted with a diagnosis of delirium secondary to multiple medication side effects, in particular anticholinergic side effects which included constipation in her case. Bereavement was the stressor which precipitated MDD for her which was complicated by insomnia. The challenge in management of MDD in the presence of delirium was carefully considered. This lady was slowly started on Escitalopram after she recovered from delirium. Her mood improved after a few weeks of treatment. Her function needed a period of rehabilitation to improve. However, her cognition did not show full recovery. Depression may have precipitated an earlier presentation of neurodegenerative disorder for this patient.

### **Conclusion**

Depression is common among the older adult, and the diagnosis is often missed by physicians, especially in the setting of dementia and delirium. Missing a diagnosis of depression causes caregiver stress and morbidity for the patients as it often leads to extensive investigations for the somatic complaints which accompany MDD. Establishing a firm diagnosis of MDD is essential to facilitate more rapid treatment. Antidepressants are generally well tolerated among the older adult, and response is quick, unless the diagnosis was incorrect. Once response to treatment is established, antidepressants can be gradually weaned off while monitoring for relapse and suicide risk.

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