Lifting the dark clouds of depression in old age.

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Abstract

About one in ten older people are affected by major depression, especially those with chronic medical illnesses and/or cognitive impairment. Late-life depression has a major impact on the affected person, his or her caregiver, the health system and the wider society. The elderly population is particularly at risk of being underdiagnosed and inadequately treated. Assessment should seek to diagnose late-life depression, to identify factors interacting with the mood disorder, self-harm or suicide risk and any features of cognitive or functional impairment. Treatment is usually multimodality involving lifestyle modification, psychotherapy and pharmacotherapy. Electroconvulsive therapy may be indicated in older people with severe or treatment-resistant depression. Management of late-life depression must always take into account coexisting medical illnesses together with their bidirectional effects on depression and cognitive impairment.

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Key Points

- Late-life depression should be diagnosed because it can be treated and should never be considered as part of normal ageing.
- The presentation of depression in older population differs from the younger population.
- Primary care physician plays an important role in assessing, treating and coordinating the care of older people with depression.
- Psychotherapy, in combination with pharmacotherapy, can be effective therapy for late life depression.

Background

Late-life depression refers to a depressive syndrome occurring in people older than age 65 years. The cut-off age is arbitrary and the condition is heterogeneous in terms of clinical features and coexisting medical disorders. As the population ages, the number of older people with depression is expected to increase and depression is predicted to become the leading cause of disease burden in middle and higher income countries by year 2030 [1]. In Australia, 10-15% of community dwelling older people experience depression and the prevalence can be as high as 35% in nursing home residents [2]. Prevalence of late-life depression is higher in hospital settings compared to primary care [3]. Older women are affected by depression twice as many as men [4]. The prevalence and incidence of major depressive disorder will double by the age of 70-85 years [5,6].

Older people may either experience recurrence of symptoms related to early-onset depression or some may experience late-onset depression. Majority are recurrences rather than first ever episodes. People with late-life depression have higher rates of coexisting medical disorders than their counterparts without depression [7]. It is associated with disability, poorer outcomes of concurrent medical illnesses and increase in mortality [7]. Furthermore suicide is almost twice as frequent in older people as in the general population, with major depression a significant risk factor [8]. Despite late-life depression being a potentially lethal disorder, people with this illness are still stigmatized, underdiagnosed and undertreated. Therefore primary care physicians have an important role in diagnosing and managing late-life depression.

This review will focus on risk factors, diagnostic evaluation and comprehensive management of late-life depression in the presence of multiple coexisting medical illnesses. Important clinical differences in presentation and management between depressions at late life compared with younger age will also be discussed.

Predisposing Risk Factors

In the evaluation of late-life depression, it is useful to identify factors that predispose, precipitate and perpetuate depressive symptomatology. Table 1 shows some of the risk factors for depression in older adults. Hereditary factors may be an important predisposing factor in a proportion of older people with depression (Table 1).

A complex bidirectional relationship is often present between depression and a coexisting medical illness. Studies have shown that medical illnesses are linked with increased risk of depression. Patients diagnosed with end stage renal failure, chronic obstructive pulmonary disease and cardiovascular disease are three times more likely to be depressed and the risk increases seven times if two or more chronic illnesses are present [9]. On the other hand, depression also adversely affects the health outcomes of those with history of coronary artery disease or stroke [10], whilst other population based cohort studies showed that depression is adversely associated with malignancy

Table 1. *Risk factors for depression in older adults.*

Physical factors
Hereditary factors
Chronic diseases (e.g. heart failure, chronic obstructive pulmonary disease, chronic kidney diseases)
Acute myocardial infarction
Cognitive impairment and dementia
Neurological disorders (e.g. stroke, Parkinson's disease)
Endocrine causes (e.g. diabetes, thyroid disease, B12 and folate deficiency)
Malignancy
Chronic pain
Medications that may cause depression
Cardiovascular drugs
Chemotherapeutics
Sedatives and antianxiety drugs
Anticonvulsants
Antipsychotic drugs
Anti-inflammatory/anti-infective agents
Stimulants
Hormones
Psychosocial factors
History of depression
Social isolation
Being a carer
Change in financial circumstances
Bereavement (e.g. loss of a spouse)
Adjustment disorder (e.g. illness, pain, disability)
Institutional care

(especially colorectal), back pain, irritable bowel syndrome and multiple sclerosis [11,12]. In this setting, clinicians often face the mammoth task of diagnosing and treating a triad of physical illness, mental illness and cognitive impairment. Furthermore, these impairments are often complex and intertwined, making it difficult to distinguish one from the other. Identification of medications associated with development of depression is critical and often overlooked.

Diagnostic Evaluation

The first point of contact between older people with depression and health care professionals is often in the primary care settings. Therefore it is important that primary care physicians diagnose the disorder when it is encountered and provide management that is consistent with current evidence-based clinical practice.

The diagnosis of major depressive disorder is usually based on criteria set out in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM–V) (Table 2) [13].

Recognizing depression in older people is often challenging because of their presentation [3]. The cardinal features of depression usually include low mood and anhedonia or loss of interest. Older adults are less likely to complain of low mood and reduced enjoyment but more likely to have sleep disturbances, somatic symptoms, cognitive decline, psychomotor retardation, psychosis, feeling of worthlessness and anxiety [14]. Furthermore, they may not be as willing to acknowledge their feelings or seek help from health professionals, rather choosing to attribute their symptoms to normal ageing (Table 3). In addition, some older adults often have symptoms of depression that do not meet the DSM-V criteria for major depressive episode.

Table 2*. DSM-V criteria for major depressive episode.*

Five or more of below must be present nearly every day for two or more weeks:
#Core symptom (one or more must be present for diagnosis)
1. Depressed mood or irritable most of the day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful)#
2. Decreased interest or pleasure in most activities, most of each day#
Additional symptoms
3. Significant weight change (5%) or change in appetite
4. Change in sleep: Insomnia or hypersomnia
5. Change in activity: Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Guilt/worthlessness: Feelings of worthlessness or excessive or inappropriate guilt
8. Concentration: diminished ability to think or concentrate, or more indecisiveness
9. Suicidality: Thoughts of death or suicide, or has suicide plan

Taken from Diagnostic and statistical manual of mental disorders (dsm-5®), American Psychiatric Pub [13].

Table 3. *Challenges in diagnosing depression in older adults.*

1. Atypical clinical presentations
• Chronic unexplained physical symptoms such as chronic aches and pains, constipation, dizziness, insomnia and weight loss
• Changes in cognition
• Changes in behaviour
2. Tendency to under-report or down play the depressive symptoms
3. Wrongly attributing depressive symptoms to old age, dementia or physical illness

Several assessment tools may be helpful in the early detection of late-life depression in primary care and other healthcare settings (Table 4). Many of these tools are used commonly to evaluate depression but few are well validated in older people with the exception of Geriatric Depression Scale (GDS), Patient Health Questionnaire (PHQ), Hospital anxiety and depression scale (HADS) and the Cornell scale for depression in dementia [15-18]. Severe depressive symptoms, suicidality and functional impairment are warning features that indicate urgent intervention.

Late-life depression may be both a risk factor for and a manifestation of cognitive decline [19]. It is often associated with a measurable impairment in cognition which may involve memory deficits, diminished executive function and delayed information processing [20]. Cognitive testing with the Mini-Mental State Examination (MMSE) is required in all older people with depression [21]. It may reveal deficits in visuospatial processing or memory even if the total score falls within the normal range [20]. Neuropsychological testing may be required to identify early dementia but testing should be performed when depressive symptoms have diminished to avoid negative effects on performance.

Some older people develop cognitive impairment during episodes of depression that is reversible after remission of depression, often referred to as pseudodementia [22]. However a large proportion of those with reversible cognitive impairment are left with some degree of persistent deficit after remission of depression, and about 40% have been reported to develop irreversible dementia within 3 years of follow-up [23]. Two meta-analyses have found that late-onset depression (after age of 65 years) is associated with a two-fold increased risk of dementia [24,25]. However no research has determined whether depression is a risk factor for dementia or a prodromal condition.

Table 4: *Tools used in the assessment of late-life depression.*

	Description	Sensitivity	Specificity	Validation in older people	Other comments
Geriatric Depression Scale (GDS-15) [15]	In population over 60 years, score of ≥ 5 indicates depression. Developed specifically for use in older people.	92%	54%	Well validated	Contains fewer somatic items. Not suitable for people with severe cognitive impairment.
Patient Health Questionnaire (PHQ-9) [16]	Self-reported depression assessment tool scoring each of the 9 DSM-V criteria as 0 (not at all) to 3 (nearly every day)	88%	80%	Validated among those >60 years in primary care.	
Cornell scale for depression in dementia (CSDD) [18]	Not diagnostic for depression but higher scores indicate greater need for further evaluation	N/A	N/A	Validated	Suitable for patients with cognitive impairment
Hospital anxiety and depression scale (HADS) [17]	Self-rating scale containing 2 subclasses measuring symptoms of depression (HADS-D) and anxiety (HADS-A) during the past week	80%	80%	Validated across all ages	

Older people with depression are at increased risk of suicide. The rate of suicide in this older age group is double that observed in the general population [26]. Older people who attempt suicides are more likely to die than younger people, while those who survive, the prognosis are poorer compared to those who are younger [27]. Therefore the presence of suicidal thoughts must be explored carefully.

In older people with major depression, their nutritional status is often affected adversely which can lead to increase in frailty and greater disability. Their nutritional status can be assessed initially with the Mini-Nutritional Assessment tool [28]. Relevant measurements of body composition such as weight should be recorded and reassessed regularly.

Assessment should also consider other differential diagnoses such as bipolar disorder. The patient should be asked about a history of bipolar disorder and questions about symptoms of mania include any periods of excessive energy or talkativeness, racing thoughts, needing less sleep, engaging in risky behaviors or spending too much money will need to be explored [29]. Additional evaluation is required for patients with alcohol or substance misuse. Laboratory tests should include full blood count, biochemistry, thyroid function test, serum vitamin B12 and folate.

Management

In older people with depression, the aims of treatment are to alleviate the symptoms, prevent recurrence of symptoms or suicidal ideation, improve cognitive and functional status, and help patients develop skills needed to manage their disability or psychosocial adversity more effectively. In the acute phase, treatment is intended to reduce major symptoms and prevent suicide or other self-harm behavior. In the maintenance phase, treatment is aimed at restoring the person to his or her premorbid level of function and prevents relapses. Broadly, the management of late-life depression generally involves multiple modality including lifestyle modifications, psychotherapy, pharmacological and electroconvulsive therapy (ECT).

Initially, most of these interventions can be implemented in the primary care setting. Whenever an older patient has not responded adequately to management options available in primary care, that person should be referred to a specialist psychiatric or psychogeriatric service for additional care. Some of the indications for referral include severe depression, psychosis, cognitive decline, suicidality or complex psychosocial situations.

Lifestyle modifications

Older people should be encouraged to be as physically active as they can. In a meta-analysis of seven randomized controlled trials (RCTs), exercise of moderate intensity was found to reduce symptoms of depression [30].

Other beneficial interventions include improving nutrition and encouraging healthy social interactions [20]. Depression often limits patients' ability to make lifestyle changes. Therefore these interventions usually needed in conjunction with others such as psychotherapy and pharmacotherapy.

Psychotherapy

Psychotherapies used in the management of depression usually involve cognitive behavioral therapy (CBT), problem-solving therapy, supportive psychotherapy and interpersonal therapy [31]. Psychotherapies are effective treatment for depression in older people and may even be considered as first-line therapy, depending on availability, patient preference and symptom severity. Most evidence for psychotherapy for late-life depression has been derived from older people in the younger age range who are cognitively intact and well-educated [32].

The focus of CBT is on identifying and reframing negative dysfunctional thoughts while encouraging participation in social activities. A meta-analysis of 23 RCTs involving older people demonstrated that CBT significantly reduced depressive symptoms compared with usual treatment or placement on a wait list for treatment [33]. However, CBT may be less effective in the presence of other medical illnesses or cognitive impairment

[34]. Studies have also found that CBT was as effective as other psychotherapies [33].

Problem-solving therapy involves helping people with depression to develop skills that will improve the ability to cope with adversities in life. An RCT has shown that problem-solving therapy led to greater improvement in depression compared with usual care or reminiscence therapy that involved participants evaluating and reframing past life events [35]. This form of therapy may also be beneficial in treating depression in older people with cognitive impairment [36].

Interpersonal therapy focuses on helping people to cope with role transitions, grief and interpersonal issues. In an RCT, interpersonal therapy was found to significantly reduce symptoms of depression compared with standard usual care [37]. However this approach may be less effective in people with coexisting medical illnesses [37].

Psychoeducation has also been shown to improve satisfaction in patients and their caregivers as well as treatment adherence [38]. Brief passive psychoeducation interventions are easy to implement can be applied immediately and inexpensive. They may offer a first-step intervention for those experiencing psychological distress or depression and might serve as an initial intervention in primary care or community models [39].

Standardized psychotherapy usually includes a short-term treatment phase, consisting of weekly visits for a period of 8-12 weeks. For mild depression, psychotherapy or pharmacotherapy alone, are acceptable alternatives. However for moderate or severe depression, combination therapy with psychotherapy and pharmacotherapy is the preferred treatment option for late-life depression.

Pharmacotherapy

There is evidence for the use of antidepressants in management of depression in older people. Selective serotonin reuptake inhibitors (SSRIs) are the first-line pharmacotherapy for late-life depression. A Cochrane systematic review of 32 RCTs involving people aged 55 years or above, reported that SSRIs and tricyclic antidepressants (TCAs) were equally efficacious but TCAs were associated with more adverse effects and treatment withdrawal [40]. Rates of SSRI response (defined as $\geq$ 50% reduction in severity) were 35-60%, compared with 26-40% in the placebo group [41,42]. A meta-analysis has also shown that SSRIs is superior to placebo in treating people with depression in the setting of chronic physical illnesses [43]. However there are few head-to-head comparison studies of various antidepressants in older people.

Overall SSRI is considered the safest class of antidepressant in older patients with concomitant depression and other medical illnesses (Table 4). Common side effects of SSRIs are nausea and headache, but these are typically mild [40]. The risk of hyponatremia related to SSRI use increases with age and is associated with female sex, low body weight, kidney impairment, psychosis, prescription of other hyponatremia-inducing drugs such as diuretics and medical comorbidities [44]. Monitoring the serum sodium levels may be necessary.

Serotonin-norepinephrine reuptake inhibitors (SNRIs) can be used as second-line agents when remission is not achieved with SSRIs. In randomized trials of older people, SNRIs were equally as effective as SSRIs but adverse effects were more common with SNRIs (Table 4) [45,46].

TCAs have similar efficacy to SSRIs in treating depression of later life but are less frequently used because of their adverse effects, especially on cognition [47]. However if SSRIs or SNRIs are ineffective, TCAs can be considered either as monotherapy or as augmentation [20]. However TCAs is listed as one of the potentially inappropriate medications in the Beers Criteria list, indicating an association with high rates of adverse drug events among older people [48]. Small open-label studies support the use of buproprion and mirtazapine in late-life depression but data from RCTs are lacking [49,50].

Up to 12 weeks of treatment with antidepressants may be needed to ascertain a full response [51]. One study has found that remission can be expected in about two thirds of patients who have partial response at 4 weeks while only about one third will achieve remission although no improvement is observed initially in this same duration [51]. Even with maximally tolerated dose, 40-65% of older patients respond adequately to a single antidepressant agent, and trials of alternative antidepressants or combination of antidepressants, with or without psychotherapy are needed for some patients [52,53]. ECT may also be needed if combination drug therapy is ineffective (Table 5).

Second-generation antipsychotic medications such as olanzapine and aripiprazole are increasingly used as augmentation therapy in treatment-resistant depression in the absence of psychotic symptoms [54]. In a two-stage study of using aripiprazole as an augmentation therapy compared to placebo in addition to venlafaxine, significantly higher remission was achieved with aripiprazole (number needed to treat of 6.6) [55]. However data is still lacking on safety with using antipsychotics long-term for treatment-resistant late-life depression. Akathisia and other extrapyramidal movement disorders are the most common adverse effects of these antipsychotic agents [20]. Other augmentation agents include buproprion and lithium. However lithium use in older people is limited by kidney function, potential for drug-drug interaction and adverse effects such as tubulointerstitial nephritis, nephrogenic diabetes insipidus and hypothyroidism [29]. Medications for symptom control (i.e., hypnotics and anxiolytics) may be useful for short periods, but prolonged use is to be avoided.

Electroconvulsive therapy

With severe depression that fails to response to adequate doses of antidepressants, ECT is the most effective treatment, including for older people. ECT is usually administered as a series of 6-12 treatments in an inpatient psychiatric setting over a period of 2-4 weeks. The indication for ECT is when there is life-threatening refusal of fluid and food intake, catatonia from psychosis and severe suicidal ideation. In late-life depression, RCTs have shown that ECT has an efficacy of 60-80% [56,57]. With the exception of raised intracranial pressure, there are no absolute contraindications to ECT although there are a number of clinical situations (e.g. uncontrolled hypertension, recent myocardial infarction, intracranial pathology, skull defect or epilepsy) in which extra caution is required.

Common short-term side effects include headache, postictal

Table 5. *Antidepressants used in the treatment of late-life depression.*

Drug	Starting dose	Maximum dose	Advantage	Side effects
Selective Serotonin Reuptake Inhibitor				
Escitalopram	5 mg daily	20 mg daily	Well tolerated. Non-sedating. Preferred for older adults	Risk of prolong QT Hyponatremia
Citalopram	10 mg daily	20 mg daily		
Sertraline	12.5 mg daily	100 mg daily	Non-sedating	Diarrhea Hyponatremia
Fluoxetine	5 mg daily	60 mg daily	Do not need tapering due to long half life	Significant drug interactions. Prolong half life
Paroxetine	10 mg at night	40 mg at night	Useful for insomnia	Weakly anticholinergic. Constipation, dry mouth or drowsiness
Serotonin Noradrenaline Reuptake Inhibitor				
Venlafaxine (XR)	37.5 mg daily	225 mg daily	Useful for co-morbid neuropathy	Increase BP. Nausea (especially with immediate release)
Venlafaxine (IR)	37.5 mg twice a day	150 mg twice a day		
Duloxetine	10 mg daily	60 mg daily	Low risk insomnia	Significant drug interactions
Atypical				
Mirtazapine	7.5 mg daily	60 mg mane	Low risk sexual dysfunction. Appetite stimulant	Weight gain. Drowsiness

confusion with both anterograde and retrograde amnesia. To reduce this risk, unilateral electrode placement with brief pulse is preferred, especially in the elderly [20]. Cognitive symptoms usually resolve following completion of ECT. Risk of ECT-associated memory problems is increased in people with cardiovascular or neurological diseases [57]. The mortality rate related to ECT is extremely low, less than one death in 10,000 patients [20]. A successful course of ECT should be followed by maintenance pharmacotherapy because of high rates of relapse [58].

Suicide Prevention

Suicide ideation decreases with age but if older people have suicidal thoughts, they are at higher risk of committing suicide than younger people [59]. Suicidal ideation is closely related with severity of depression [59].

Suicide risk assessment by primary care clinicians is often inadequate at the last clinical review prior to a person dying by suicide [60]. Ambivalence, worthlessness, helplessness and hopelessness are key indicators of heightened suicide risk [61]. The Columbia Suicide Severity Rating Scale is a useful tool to establish the risk of suicide [62].

In addition to treatment of depression, interventions to decrease isolation and augment social support through activity groups and telephone outreach among older people are ways that can reduce mortality associated with suicide [63]. Older people manifesting acute suicidal behaviors usually require interventions that will ensure safety including the need for hospital admission [61].

Maintenance Treatment and Prognosis

Late-life depression is a recurrent disorder. In one study, 90% of older people with late-life depression in remission experience recurrence within a year when not maintained on therapy [64]. Longitudinal studies have shown that continued treatment with an antidepressant alone or combined with interpersonal psychotherapy, after remission provided sustained benefit [64,65]. For maintenance, antidepressants should be used at the same doses as for treatment. Older patients with a single episode of severe depression, antidepressant therapy should be continued for at least a year. For patients with three or more lifetime episodes, maintenance therapy is likely to be required for longer than three years [22]. Monitoring patients' adherence to treatment is an important aspect of long-term management.

Managing Comorbidities

Medical comorbidities are highly prevalent in people with late-life depression because of genetic vulnerability, life-style factors (e.g., smoking, malnutrition and lack of physical activity) and sometimes arising from adverse effects of pharmacological treatment. In view of the bidirectional relationship between comorbidities and late-life depression, regular monitoring of weight, blood pressure, electrolyte, renal function, plasma glucose, liver function and lipid profile, are indicated. Overall, regular reassessment of the risk-benefit balance of each treatment is recommended in addition to consideration of other strategies when clinically significant adverse effects occur.

Conclusion

Depression is a treatable condition and should never be considered a normal part of aging. Therefore, it is crucial to understand and recognize the symptoms of the illness in primary care, especially among older patients with multiple medical comorbidities. The treatment of depression requires patience and perseverance from patients and treating clinicians. Sometimes several different treatments may have to be tried before full recovery. Nevertheless, close liaison and collaboration between general practitioners, psychiatric services and other health professionals helps promote identification and appropriate treatment of late-life depression.

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