

Late-life depression: issues for the general practitioner

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Abstract: Late-life depression (LLD) is both a prevalent and life-threatening disorder, affecting up to 13.3% of the elderly population. LLD can be difficult to identify because patients mainly consult their general practitioner (GP) for somatic complaints. Moreover, patients may be hesitant to express the problem to their GP. Increased vigilance on the part of the GP can only benefit older people with depression. To recognize the risk of LLD, screening tools are provided in addition to treatment options for LLD. This review aims to provide the GP with guidance in recognizing and treating LLD. It tries to connect mainstream etiologies of LLD (e.g., vascular, inflammation, hypothalamo–pituitary–adrenal axis) with risk factors and current therapies. Therefore, we provide a basis to the GP for decision-making when choosing an appropriate therapy for LLD.

Keywords: geriatric mental health, major depressive disorder, elder care, psychosomatic, geriatric psychiatry

Introduction

Late-life depression (LLD), with an estimated prevalence of 13.3%, is a common mental health disorder in older people.¹ It is associated with increased morbidity and mortality in addition to a high societal cost.² Moreover, the treatment cost of an older person with depression is 1.86 times higher than that of an older person without depression.³ The consequences of untreated LLD include poor quality of life, exacerbation of chronic illnesses, and suicide.⁴ Due to the atypical presentation, the diagnosis is often missed by general practitioners (GPs), which consequently leads to undertreatment of the disease.⁵ However, an LLD diagnosis in time can be life-saving and, when treated, LLD has a good prognosis; up to 70% of older patients with depression treated with antidepressants recover from a depressive episode.⁶ The aim of this review is to provide a comprehensive and practical guide for GPs with regard to the main risk factors as well as the diagnostic and therapeutic approach to LLD.

Definition of the problem

LLD can be defined as depression that occurs for the first time after age 60. When we use the term “depression”, we refer to major depressive disorder as defined by the *Diagnostic and Statistical Manual of Mental Disorders 5* (DSM-5). The cardinal symptoms of major depressive disorder are anhedonia (a loss of interest in activities one used to enjoy) and a depressed mood through most of the day.⁷ According to the

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DSM 5, an older person has an episode of major depression if he or she has at least one cardinal symptom and four or more of the following symptoms for at least 2 weeks: significant decrease or increase in weight or appetite; insomnia or hypersomnia, fatigue, psychomotor agitation, or retardation; diminished ability to concentrate or make decisions; feelings of worthlessness or inappropriate guilt; and recurrent thoughts of death or suicidal ideation. In the elderly, depressive feelings may often be masked by unexplained physical complaints (e.g., fatigue, diffuse pain or back pain, headache, chest pain, etc.) and, consequently, the classical DSM 5 criteria sometimes seem to fail in terms of diagnosing depression in elders.⁸

Furthermore, the conditions mentioned above can exist concomitantly. The differential diagnosis of LLD is broad (Table 1). Physical examination and cognitive screening may be useful in ruling out common conditions that are often confused with depression and in assessing for commonly co-occurring diseases. Consequently, a thorough medical history, Mini Mental State Exam, physical examination, and, sometimes, further technical investigations are recommended. Indications for referring patients to a geriatric psychiatrist are presented in Table 2.⁸

A particularly difficult differential diagnosis of LLD is dementia (see Table 3). Moreover, Parkinson disease (PD) is a prevalent neurodegenerative disease associated with depression and occurs in up to 35% of patients with PD.¹⁰ Depression associated with PD is not a single entity, but rather a heterogeneous group of three subtypes where only one group is directly related to the pathophysiology of PD.¹¹ The signs of depression linked to PD include nonresponse to at least one course of antidepressant treatment, absence of suicidal behavior, absence of guilt and self-blame, and no personal history of depression. The pathophysiological mechanism of depression in PD is unknown, but a current hypothesis

Table 1 Differential diagnosis of late-life depression

Central nervous system disorders (dementia, Parkinson disease, and neoplastic lesions)
Related psychiatric disorders (dysthymia, bipolar, and anxiety disorders)
Endocrine disorders (hypothyroidism, hyperthyroidism, and hyperparathyroidism)
Adverse events of some pharmacological agents (e.g., β -blockers, centrally active antihypertensive medications, steroids, H ₂ -blockers, sedatives, certain chemotherapy agents)
Life circumstances (e.g., grief, bereavement, financial loss)
Substance use, abuse, or dependence
Infectious and inflammatory diseases (e.g., HIV encephalopathy, systemic lupus erythematosus) and sleep disorders (in particular, obstructive sleep apnea)

Note: Data from Fountoulakis et al.⁹

Table 2 Summarizing table

Patients at risk for late-life depression		
<ul style="list-style-type: none"> Poor physical health and frailty Female gender Oldest elders (≥ 80 years) Cognitive impairment and neurodegenerative disease 	<ul style="list-style-type: none"> Nutritional deficits Vascular events Lifestyle: smoking, alcohol, multiple medications Being single or widow(er) 	
Screening tools		
GDS	CES-D	PHQ2
<ul style="list-style-type: none"> Yes/no format Takes 3–4 min to complete Validated for the oldest elders and MMSE >10 Preferred screening tool for Parkinson disease Cutoff 30-item list: 10–19, mildly depressed 20–30, severely depressed Cutoff 15-item list: ≥ 5, major depressive disorder 	<ul style="list-style-type: none"> Scoring statements with 0–3 scores Takes 5 min to complete Validated in patients suffering from dementia Cutoff: ≥ 20, major depression 	<ul style="list-style-type: none"> Two yes/no questions Takes <1 min to complete If positive, further investigations are necessary
Treatment options based on stepped care		
Nonpharmacological	Pharmacological	ECT
<ul style="list-style-type: none"> Psycho-education Psychotherapy <ul style="list-style-type: none"> Patients who prefer talking over medication As adjunctive therapy Structured physical exercise <ul style="list-style-type: none"> Frequency: 3–4 times a week One session: 45–60 min 	<ul style="list-style-type: none"> Substitution therapy (when deficit is present) <ul style="list-style-type: none"> Vitamin D: 2,000 IU daily Folic acid: 800 μg–2 mg Antidepressants <ul style="list-style-type: none"> SSRIs (e.g., sertraline) TCAAs (e.g., nortriptyline) SNRIs (e.g., duloxetine, venlafaxine) Mirtazapine 	<ul style="list-style-type: none"> Reserved for <ul style="list-style-type: none"> Oldest elders (≥ 80 years) Treatment-refractory depression Psychotic depression Depression with severe weight loss and anorexia Psychomotor agitation or retardation

Consider referral to a mental health specialist: preference nonpharmacological treatment, persistent depression (one to three trials of antidepressants), psychosis, mania, or concern about suicide

Abbreviations: GDS, Geriatric Depression Scale; CES-D, Center for Epidemiologic Studies; PHQ2, Patient Health Questionnaire; MMSE, Mini-Mental State Examination; ECT, electroconvulsive therapy; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; SNRIs, serotonin–norepinephrine reuptake inhibitors.

implies genetic factors, Lewy body pathology, stress-induced hypercortisolemia, inflammation, psychosocial aspects, and changes in monoaminergic signaling.¹⁰

In the assessment of LLD, exclusion of somatic causes of depression through patient history, clinical examination, laboratory tests, and/or imaging is the first step in appraising LLD.¹² A GP who has good knowledge of the patient’s personality can identify nonverbal cues and changes in behavior suspicious for mood problems.¹³ In addition, information from family members and/or caregivers on the patient’s mood,

Table 3 Differential diagnosis: late-life depression versus dementia

	Late-life depression	Dementia
Onset	Slow or acute	Slow and progressive onset
Evolution	Chronological order of events can be recalled	History of the disease cannot be restored by the patient
Quality of life (as experienced by the patient)	Decreased	The patient does not experience his/her disease as a problem
Memory	Decreased ability to think or concentrate or being slowed down	Decreased Impaired ability to learn new information or to recall previously learned information Patient tries to hide cognitive problems
Language and praxis	Normal	Decreased
Affect	Apathetic, depressed mood, psychomotor retardation	Lability of affect
Somatic	Sleep disturbances Somatic problems (insomnia, dizziness, pain, etc.) Low energy Diurnal mood variation	Can be present, but will not be chief complaint
Prognosis	Treatable	Irreversible

functioning and behavior is crucial for assessing the older person with depression.

There is no golden standard for bringing up depression; it is dependent on the physician's manner, and research on the topic is lacking. To engage the patient, the use of the bio-psychosocial model may be helpful: inform the patient that the illness is an interaction between physiological (e.g. serotonin hypothesis), psychological, and social factors.¹⁴

Risk factors

The risk factors for LLD are a combination of biological and psychosocial factors.

Biological risk factors

The biological risk factors associated with LLD are old age and female sex.¹⁵ In addition, there may be a genetic vulnerability, making some people more susceptible to LLD than others.¹⁶

Patients with poor physical health (e.g. multiple comorbidities, sleeping disorders, etc.) may be predisposed to LLD.¹⁷ These people often use more medication, which in itself is a risk factor for LLD.¹⁸

The concept of frailty stresses a loss of function in several domains of functioning (not only the physical), leading to a decline in the reserve capacity for dealing with stressors. Frailty can be defined by the Fried criteria: weight loss, decreased handgrip strength, slowness, exhaustion, and low physical activity.¹⁹ Physical frailty is linked to chronic inflammation and LLD.^{20,21} Poor nutritional status is associated with frailty; therefore, nutritional supplements (vitamin D and proteins) could benefit the depressed frail patient.²² Nutritional deficits that are often reported in older people

with depression are vitamin B12 and folate deficiencies.²³ The current hypothesis states that vitamin D affects mood by interacting with brain receptors in the limbic structures and hippocampus.²⁴

Neurodegenerative disease (e.g., PD or Alzheimer) and mild cognitive impairment (MCI) has also been considered a possible risk factor for LLD.²⁵ There are hypotheses that LLD may lead to MCI and, consequently, dementia.²⁵ The debate is still ongoing, and the current literature is inconclusive about LLD being a prodrome of dementia.²⁷ What we do know is that LLD and dementia frequently co-occur, and depression can be the first sign of dementia.^{28,29}

The vascular hypothesis states that cerebrovascular disease may cause or predispose to LLD. The concept of vascular depression as a clinical entity is inherently linked to this hypothesis and can be explained by reduced cerebral perfusion, altered brain connectivity due to vascular brain lesions, and chronic low-grade inflammation.³⁰ LLD has been linked to atherosclerosis, which is – at the same time – the leading cause of coronary heart disease.³¹

Psychosocial risk factors

Kaji et al point out that psychological factors such as loss of purpose in life or human relationships seem to be associated with LLD.³² Moreover, lower education has been linked to LLD.³³ Being a widower or single is a risk factor for LLD, but possibly reflects the fact that loneliness, lack of social support, and stressful life events or poverty are the risk factors for depression in old age.³⁴ Being functional or visually impaired increases the risk of developing LLD.³⁵

Poor lifestyle habits can put elders at risk for LLD. Both smoking and alcohol use are the risk factors of LLD.¹⁸ In

addition, the use of sleep medication has been linked to LLD, but sleep disturbance in general is a risk factor for LLD.³⁵

Screening

In the following text, we only discuss screening tools validated in a geriatric and primary care setting. These tools should not be used systematically; rather, an opportunistic screening is advised in patients in whom LLD is suspected. In Table 4, we compare the Geriatric Depression Scale (GDS), Center for Epidemiologic Studies Depression Scale (CES-D), and Patient Health Questionnaire 2 (PHQ-2).

Approach

The recommended approach to LLD is stepped care: treatment is based on the severity of depression and preference of

the.⁴² The severity of the depressive disorder (mild, moderate, or severe) is based on the number of symptom criteria, the severity of those symptoms, and their functional disability in the DSM-5. If the selected treatment for LLD is inadequate, the GP should step up and provide the next step of treatment (see Figure 1). A summary of risk factors, screening tools, and interventions are provided in Table 2.

Prevention

The risk factors that can be modified are nutritional deficiencies and cardiovascular disease, which are more common at older ages.^{43,44}

Vascular risk factors can be improved by exercise, diet, smoking cessation as well as treatment for hypertension, hypercholesterolemia, and hyperglycemia.^{45,46} These inter-

Table 4 Comparison of validated screening tools for late-life depression in primary care

	Geriatric Depression Scale (GDS)-15 ³⁶	Center for Epidemiologic Studies Depression Scale (CES-D) ³⁷	Patient Health Questionnaire 2 (PHQ-2) ³⁸
What	Yes/no questionnaire	A short self-report scale of 20 statements, divided into multiple categories, designed to measure depressive symptoms over the past week	Questions depressed mood and anhedonia in the previous 2 weeks
Cutoff	5	25	Positive response to one of the two questions
Sensitivity	79%–100% ³⁷	85% ³⁹	100% ⁴
Specificity	67%–80% ³⁷	64% ³⁹	77% ⁴
Time to complete	3–4 min	5 min	1 min
Extra	1. Validated in the oldest elder (≥80 years) with cognitive impairment (lower limit: Mini-Mental Status Exam 10) ⁴⁰ 2. Preferred screening instrument in Parkinson patients	Can be used for patients with dementia (average Mini-Mental Status Exam score of 19) ⁴¹	



Figure 1 Stepped care approach to late-life depression, based on the severity of depression and patient preference. Initiate the next step if the patient does not respond to the therapy.

ventions reduce the further progression of atherosclerosis and prevent diabetes and cerebrovascular disorders – all of which are linked to LLD.^{45,47}

Nutritional supplementation, such as a high dose of vitamin D (2,000 IU daily), folic acid (800 µg–2 mg), and a high-protein diet (for frail elders), for a deficiency of vitamins or folic acid in older people (including the frail) with depression has been suggested to alleviate depressive symptoms.^{22,24,48}

Nonpharmacological treatment

Psycho-education

The GP plays a central role in providing psycho-education: to clarify major depressive disorder, to explain therapeutic options, discuss biopsychological vulnerability, to teach to recognize warning signs, and to inform and support the spouse.⁴⁹ In addition, the primary physician actively monitors the patient through frequent visits. Moreover, the primary physician tries to provide a structure in the patient's life and activate the patient through structured and fun activities.⁵⁰ The structure provided must be manageable for the patient and should lead to positive feelings. A balance between tasks and relaxation is essential. Healthy food, sufficient sleep, and daily interactions are a prerequisite.

Behavioral activation

Structured physical activity is recommended for older people with mild or moderate depression who are physically capable and can be motivated to exercise.⁵¹ Exercise is safe and effective in addition to the pharmacological treatment of depression.⁵¹ Mere referral of an older person with depression is not enough.⁵² Primary care physicians and psychiatrists should take an active role in keeping the patient motivated and managing the exercise-related adverse effects.⁵³ A recent meta-analysis recommends structured, supervised exercise programs, three times a week (45–60 min), over 10–14 weeks, and at low intensity for mild to moderate depression.⁵¹

Psychotherapy

Psychotherapy is the most important type of nonpharmacological treatment. In LLD, psychotherapy decreases depressive symptoms in older people with depression.⁵⁴ Psychotherapeutic interventions can prevent LLD in older people with sub-syndromal depression⁵⁵ and are not inferior to pharmacological treatment.⁵⁶ Evidence-based psychotherapeutic treatments of depression in older adults include cognitive behavioral therapy (CBT), problem-solving therapy (PST), reminiscence therapy, and interpersonal therapy (IPT).⁵⁷ One relatively new therapy is life review therapy,

where the patient shares and talks about important life events and memories with their therapist. A randomized controlled trial (RCT) proved that life review therapy is effective in depressed older adults and also reduces anxiety.⁵⁸ In addition, life review therapy has already been implemented with success in a structured multidisciplinary approach in nursing homes and led to reduced prevalence of depression.⁵⁰

Pharmacological treatment

Older adults have different pharmacodynamics and pharmacokinetics due to age-related physiological changes.⁵⁹ Medication must be administered at lower doses or slowly titrated while actively monitoring the patient.⁶⁰ Patients with comorbidities usually take multiple drugs. Increased vigilance for drugs interactions is, therefore, necessary.⁶¹ A careful review of the patient's drug history is recommended. Moreover, when choosing a psychotropic drug, one needs to keep track of the drug's safety profile. Because falls can invalidate old adults and even lead to increased mortality (hip fracture), avoid medications that sedate the patient.^{62,63}

In primary care, both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are the pharmacological treatments of choice.⁶⁴ Existing evidence suggests that no one class of antidepressant drugs has been found to be more effective than another in the treatment of LLD.⁶⁵ Although newer antidepressants are not more effective than older ones, they are better tolerated and are safer, especially in cases of overdose.⁶⁰ The adverse effect data suggest the modest superiority of SSRIs over TCAs.⁶⁶ When choosing an SSRI, slight preference goes to an SSRI with the least known drug interactions such as sertraline or (es) citalopram. Citalopram has a Food and Drug Administration (FDA) black-box warning for increased risk of arrhythmia (QTc prolongation), which is why sertraline is preferred over citalopram.⁶⁷ TCAs are as effective as SSRIs for LLD, but are less often used because of frequent side effects.⁶⁸ TCAs with lesser anticholinergic side effects, such as nortriptyline, are recommended by the authors. Both SSRIs and TCAs are associated with fracture risk, although causality is not proven.⁶⁹

Serotonin and noradrenaline reuptake inhibitors (SNRIs; e.g., duloxetine, venlafaxine) are an alternative to SSRIs for depressed older adults when SSRIs are ineffective or contraindicated.^{70,71} SNRIs are not only effective against the major depressive disorder but also effective in the treatment of peripheral neuropathic pain.

Another second-generation antidepressant that can be used as an alternative for SSRIs is mirtazapine. The sedative side effects of mirtazapine are used as a treatment for

insomnia.⁷² In addition, mirtazapine improves the appetite and can be used for anorexia.⁷³ The effect of mirtazapine on sodium levels is limited, and therefore, less hyponatremia is noted in patients taking mirtazapine.⁷⁴

Important and frequent side effects and contraindications of antidepressants are reported in Table 5.

Electroconvulsive therapy

An effective treatment for LLD, available from mental health specialists, is electroconvulsive therapy (ECT). In ECT, an electrical stimulus is given for a brief period to produce a generalized seizure. Multiple RCTs have proved that ECT is beneficial for LLD, especially psychotic depression, treatment-refractory depression, catatonia, and depression with severe weight loss and anorexia.^{75,77} ECT is an effective and safe treatment for depression in adults, including the oldest elders (≥80 years).⁷⁷ Recent evidence suggests old age is a positive predictor of response to ECT: it gives faster and higher remission rates as compared to antidepressants.⁷⁸ A meta-analysis of the cognitive effects of ECT

suggests its relative safety and the transient character of its effects on memory.⁷⁹ Autobiographical memory is affected by ECT, but restored or improved 6 months after treatment.⁸⁰ Compared to antidepressants, ECT induces a higher speed of remission.⁸¹

Multidisciplinary approach

A multidisciplinary approach to LLD can be achieved through a collaborative care model. Collaborative care was designed in the United States for patients with (chronic) depression, wherein the GP who cares for a depressed elder is supported by a care manager and a multidisciplinary team comprising a psychiatrist and nurses. In this model, there is a shared responsibility of the depressed patient and the patient can benefit from different albeit synergistic approaches of LLD. Collaborative care is more effective than the standard care by GPs and was successfully tested in the United States, England, and the Netherlands.^{82–85} In general practice, the patient and his close family members can be invited once or twice a year to a “home meeting”. Those present at these meetings are the most relevant caregivers: the physiotherapist, the social worker, the home nurse, the occupational therapist, and the GP. In this meeting, the patient can express his/her needs, whereas the other members can balance what’s going well with what can improve the treatment of the patient. These recommendations then guide the treatment plan. If deemed necessary, the patient can be extensively investigated in a geriatric day-care hospital. In a few cases of severe and recurrent depression, a case manager (e.g., working in a geriatric psychiatric clinic) can be asked to coordinate the implementation of the defined treatment plan.

Table 5 Side effects and relative contraindications of antidepressant treatment

	Important and frequent side effects	Relative contraindications
SSRIs	<ul style="list-style-type: none"> Gastrointestinal irritation, nausea, or diarrhea Parkinsonism Increased risk of gastrointestinal bleeding (due to direct effect of serotonin on platelets) Hyponatremia (due to syndrome of inappropriate antidiuretic hormone secretion) Falls and fractures Serotonin syndrome 	<ul style="list-style-type: none"> Bipolar disorder Hypersensitivity Concomitant use of monoamine oxidase inhibitors
TCA's	<ul style="list-style-type: none"> Anticholinergic symptoms (constipation, dry mouth, blurred vision, and retention of urine) Arrhythmia Orthostatic hypotension Falls and fractures 	<ul style="list-style-type: none"> Recent myocardial infarction Heart failure Arrhythmias Glaucoma
SNRIs	<ul style="list-style-type: none"> Gastrointestinal irritation Sexual side effects Headaches Excessive sweating Hypertension 	<ul style="list-style-type: none"> Disturbed liver function Renal clearance <30 mL/min Uncontrollable hypertension
Mirtazapine	<ul style="list-style-type: none"> Sedation Increased appetite and weight Dry mouth 	<ul style="list-style-type: none"> Use of monoamine oxidase inhibitors Hypersensitivity

Abbreviations: SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; SNRIs, serotonin–norepinephrine reuptake inhibitors.

Conclusion

LLD is a prevalent disease that often presents with atypical symptoms and more somatic (co)morbidities and complaints. A stepped care model to treat depression is advised, taking into account the severity of the depression. Due to the somatic co(morbidities), a collaborative care model is preferred. The collaborative care model has proven efficacy and cost-effectiveness in LLD.

Disclosure

The authors report no conflicts of interest in this work.

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