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Review

Treatment of late-life depression

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Abstract

Background: Late-life depression is a major cause of morbidity among the elderly. It is often underdiagnosed and undertreated, and several factors make the management challenging. **Aim**: This paper aims at identifying various factors associated with the treatment of depression in the elderly. **Method:** A comprehensive literature review of recent relevant publications has been done. **Results:** The treatment approach for late-life should be multimodal encompassing biological, psychological, and social interventions. A comprehensive geriatric assessment should be completed for those suspected of depression. Specialist mental health care and inpatient treatment may be required when there are high-risk factors associated with the presentation including persistent suicidal thoughts, self-neglect, psychotic symptoms, and severe agitation. Appropriate use of relevant mental health act and medicolegal framework need to be considered. There are three phases in the treatment of depression: (i) acute phase, (ii) continuation phase, and (iii) maintenance phase. There is relatively little data on the use of antidepressants in older patients. Caution should be exercised while prescribing antidepressant medications in the elderly. Comorbid medical conditions put patients at a higher risk of side effects, and being on several medications increases the chances of drug interactions. Physical treatments like Electro Convulsive Therapy (ECT) do play a major role in the treatment of depression in the elderly. Psychological interventions have been found to be effective. **Conclusion:** The judicious use of antidepressant medications and ECT as part of a multimodal approach is beneficial in the treatment of depression among the elderly. There is a need for further studies that look specific factors associated with the treatment of depression in the elderly.

Key words

Antidepressants, Depression, Elderly, Late-Life

Introduction

Depression among the elderly is often underdiagnosed and undertreated. Late-life depression can be treated effectively with pharmacological and psychological interventions. With a higher relapse rate than the younger population and coexisting physical problems, treatment of depression among elderly warrants special attention. Though the management principles are shared across age groups, specific biological factors like changes in metabolism and poor psychosocial support among the elderly need to be factored in. In this paper, we discuss the pharmacological and psychological treatments for late-life depression. A comprehensive literature review of recent relevant publications has been done for this article.

Box 1: Pre-treatment evaluation

- The elderly presenting with the first episode of depression should have a full medical work up to rule out any medical disorders.
- Haemogram / Full Blood Count, fasting glucose, urine analysis, electrolytes, liver function tests, renal function tests, ECG, B12 and folate, thyroid function tests, calcium, lipid profile are recommended.
- Physical examination to exclude nutritional deficiency, anaemia, and thyroid abnormalities should be routinely done.
- Neuroimaging need to be considered in first episode depression, treatment-resistant depression, and when the patient has neurological signs or present with cognitive impairment.
- Further investigations should be directed by the nature of the presentation and clinical findings.
- Cognitive assessment should be completed where appropriate.
- Especially in those with cognitive impairment and dementia, delirium should be ruled out.

Pre-treatment evaluation and investigations

A comprehensive geriatric assessment should be completed for those suspected with depression.[1] Detailed treatment history, including antidepressants and other medications used in the past, response to them and side effects, compliance, and tolerability, and patient's views about medications need to be taken. Treatment history of other physical problems and medications used and the relationship between their use and depression, including potential drug interactions, are important as well.

Box 2: Summary of NICE guidelines for the treatment of depression

***Persistent sub-threshold depressive symptoms or mild to moderate depression**:*

- Low-intensity psychological interventions
- Consider antidepressants if there is a past history of moderate or severe depression or initial presentation of sub-threshold depressive symptoms present for at least 2 years or sub-threshold depressive symptoms or mild depression persisting after other psychological interventions or for people with depression and a chronic physical health problem, if mild depression that complicates the care of the physical health problem.

Persistent sub-threshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions, and moderate and severe depression:

- Antidepressant or a high-intensity psychological intervention like CBT or interpersonal therapy (IPT)

For people with moderate or severe depression:

- Combination of antidepressant medication and a high-intensity psychological intervention (CBT or IPT)

Complex and severe depression:

- Secondary care multidisciplinary mental health services where options include inpatient care, full range of high-intensity psychological interventions, medications, electroconvulsive therapy, etc.

People with chronic physical health problems:

- Consider the role of the physical health problem and any prescribed medication in the depression. Check that the optimal treatment for the physical health problem is being provided and adhered to; seek specialist advice if necessary.

Treatment

There are three phases in the treatment of depression: (i) acute phase – is the time from initiation of treatment to remission, i.e., patient does not meet the criteria for diagnosis and has no or minimal residual symptoms and, has an improvement in psychosocial and occupational functioning; (ii) continuation phase – this phase aims to preserve and stabilize the remission – here, treatment is extended for a period of time in order to prevent a return of depression. If the depressive syndrome returns during the continuation therapy, it is considered a relapse of the same episode. It is sometimes difficult to differentiate between a relapse and a recurrence (is a new episode of depression); (iii) maintenance phase - aims to prevent the recurrence of depression as well as to enable full and lasting functional recovery.[2]

A comprehensive treatment package can include anti-depressant medication, electro-convulsive therapy (ECT), psychological interventions, social interventions, and measures to address psychiatric comorbidity and medical problems if any. Specialist mental health care and inpatient treatment may be required when there are high-risk factors associated with the presentation, including persistent suicidal thoughts, self-neglect, psychotic symptoms, and severe agitation. Appropriate use of relevant mental health act and medicolegal framework need to be considered. For many elderly, an in-patient admission might be their first experience of a psychiatric ward, and the psychological and social impact this can have should be given due consideration. As the evidence base for treatment of depression, specifically in the elderly, is limited,[3] most treatment guidelines do not distinguish between depressed adults and the elderly depressed. Hence, general guidance on treating depression in adults needs to be followed in a stepped care/ algorithmic approach with due age-sensitive precautions. A summary of the UK National Institute for Health and Clinical Excellence (NICE) guidelines for the treatment of depression is given in Box 2.[4,5] It advises to prescribe an age-appropriate dose when prescribing antidepressants for older people, taking into account the effect of general physical health and concomitant medication on pharmacokinetics and pharmacodynamics, and to carefully monitor for side effects.

Choosing an antidepressant

There is relatively little data on the use of antidepressants in older patients, especially in the very old and in those with significant medical co-morbidity, dementia, or neurological problems, and there is considerable heterogeneity between studies.[2] Physiological changes associated with ageing can affect drug distribution within the body and excretion. Comorbid medical conditions put patients at a higher risk of side effects, and being on several medications increases the chances of drug interactions. Factors such as a history of good response to past treatment, fewer side effects and good tolerability, and minimal interactions with drugs that are currently being taken and which least affect the general medical conditions help choose the antidepressant. The aim of the treatment of depression ought to be complete relief of symptoms (remission) with improved functioning and a better quality of life. Prescribers can use resources such as a drug's 'summary of product characteristics' (SPC) and the 'British National Formulary' (BNF)[6] to make informed decisions with each patient. The doctor should support the patient in making treatment choices by providing adequate information and informing that it can take up to a few weeks to start feeling better.

(a) Antidepressant classes

Major classes of antidepressants include selective serotonin reuptake inhibitors (SSRIs: sertraline, citalopram, escitalopram, fluoxetine), serotonin norepinephrine reuptake inhibitors (SNRIs, e.g. venlafaxine and duloxetine), tricyclic antidepressants (TCA, e.g. nortryptiline, amitriptyline, lofepramine, etc.) and mono amine oxidase inhibitors (MAOs, e.g. phenelzine, reboxetine, etc.). Others include mirtazapine, bupropion, vortioxetine, agomelatine, and so on.

(b) Dosing strategies

Selective serotonin reuptake inhibitors (SSRIs) are the standard first-line treatment for depression;[4] and sertraline, escitalopram, and citalopram are commonly prescribed; (citalopram increases the risk of QT prolongation). Older patients are typically started on a lower oral dose than younger adult patients, and it may be necessary to titrate doses for effectiveness. Higher plasma concentrations for a given dose are generally found in older compared to younger patients and doses may need to be adjusted particularly in patients with impaired renal or liver function.[2] If the side effects are not tolerable, change to a different antidepressant depending on the nature of the side effects. A recent guideline[7] also supports the use of an SSRI or SNRI as first-line treatment, similar to earlier guidelines.[2,8,9] Mirtazapine can be a first-line alternative when SSRIs cannot be used. Side effects of mirtazapine, such as increased appetite and weight gain, can be used to the benefit of some patients.

After 2 weeks of being on an antidepressant, treatment response should be evaluated, and if insufficient, optimization strategies should be implemented. In the absence of improvement after at least 2 weeks on an average dose of an antidepressant, increase the dose gradually up to the maximum recommended dose if well tolerated until clinical improvement, or limiting side effects are observed.

(c) Switching and augmentation strategies

Consider changing the antidepressant after at least 4 weeks at the maximum tolerated or recommended dose if there is no or minimal response, and after 4 to 8 weeks if there is only a partial response.[9] In patients with only a partial response, switch to another antidepressant of the same or another class while considering the risk of losing the improvements made with the first treatment. At least 8 to 10 weeks may be required to achieve maximum symptom reduction, which is necessary before entering the continuation phase of treatment.[2] In severe depression with psychotic features, adding an antipsychotic such as olanzapine or quetiapine to the antidepressant is recommended. If one treatment is to be stopped during the maintenance phase, this should usually be the antipsychotic. Antipsychotics should be used with caution in those with cardiovascular disorders and those with cognitive impairment/ dementia due to an increased risk of stroke. ECT should always be considered where a rapid response is required or where other treatments have failed.[10]

Improvement in depressive symptoms during the early course of treatment has been identified as being highly predictive of a positive final treatment outcome.[2] If no moderate improvement (based on clinical judgement and scores on depression rating scales) is shown within 8 weeks of good compliance with the maximum recommended dose of an antidepressant, diagnosis should be reviewed, pharmacokinetic and pharmacodynamics factors need to be assessed,[3] and clinical factors impeding treatment including general medical conditions, substance use, comorbid psychiatric conditions and psychosocial factors need to be carefully looked into. Compared to younger adults, response to antidepressant treatment may be slower in older adults with older antidepressants (such as TCAs and MAOIs) whereas there is conflicting data regarding newer antidepressants (such as SSRIs and SNRIs).[2] Although the elderly may be a little slower to respond to antidepressant treatment than younger adults, this does not appear to be clinically significant.[3]

Non-responders

About one-third of the elderly depressed patients are treatment-resistant.[11] In at least 30% of depressive episodes, patients may not respond sufficiently to an adequately performed first-line treatment with any chosen antidepressant. Helpful strategies in such cases include: maximizing the dose of the initial antidepressant, switching to another antidepressant within the same pharmacological class, switching to another antidepressant from a different pharmacological class, combining two antidepressants from different classes, augmenting the antidepressant with other agents to enhance antidepressant efficacy, and combining the antidepressant with a psychotherapeutic intervention.[2]

Second-line antidepressants include mirtazapine, venlafaxine, and so on. When the patient is weaned off the existing medication before starting the new one, there may be a loss of clinical improvement. Cross-titration (gradual reduction of the existing antidepressant while introducing and gradually increasing the new antidepressant) is an effective strategy to overcome this, but it has to be done cautiously considering potential interactions between the two antidepressants.[10] Antidepressants with short half-lives can be switched within a week; fluoxetine requires a wash-out period of several weeks due to its longer half-life. Overall about 50% of patients respond to switching or augmentation, although data specific to the elderly is small. Augmentation with Lithium has been found to be effective.[12,13] Lithium has the most evidence in support as an augmenting medication.[3] Lithium is usually recommended as the first choice and the target serum levels for elderly must be in the range of 0.5 to 0.6 mmol/L, and it needs to be continued for a period of at least 1 year after achieving remission.[14] Other augmentation/ adjunctive agents tried, include thyroid supplements, aripiprazole, psychostimulants, modafinil, etc. Combining psychotherapy or using a different psychological intervention may also be tried.

Bipolar depression

While treating bipolar depression, the clinician should also be cautious in preventing a switch to hypomania or mania. If the patient is already on a mood stabiliser, ensuring compliance and optimising it would be crucial. Lithium or lamotrigine may be used in the management of bipolar depression. Antidepressants appear to be effective in the short-term treatment of bipolar depression. Stopping antidepressants needs to be considered once bipolar depression remits. Use of antidepressants without

the use of concurrent mood stabilizer or an atypical antipsychotic may be avoided. If the patient does not respond to monotherapy with mood stabiliser or antipsychotics, a combination of these agents with antidepressants may be considered.[15,16] There have been post-hoc analyses of randomized clinical trials of lurasidone and quetiapine in which the elderly patients were examined separately, which showed that both drugs were successful and well-tolerated, suggesting that, as a class, atypical antipsychotics probably can be used in bipolar depression.[17,18]

Precautions while prescribing antidepressants

Having considered if, when, and what medications to prescribe for the treatment of depression in the elderly, clinicians need to bear several precautions in mind.[6,10,14] Some of the important precautions to bear in mind while prescribing antidepressants are summarised in Box 3.

Box 3: Precautions while prescribing antidepressants

- Depressive symptoms may get worse with antidepressants especially, during the start of treatment, titration of doses, and change of antidepressants.
- Consider the toxicity of prescribed medications in overdose and limit the amount of drugs available if the patient is at a high risk of suicide.
- Older adults are at an increased risk of reduced bone density, and falls and fractures.
- Tricyclic antidepressants have an increased risk of cardiac side effects including, postural hypotension leading to falls and fractures, cardiac conduction abnormalities, anticholinergic effects like urinary retention, dry mouth, constipation, and worsening of cognitive impairment.
- Citalopram increases the risk of QT prolongation and hence should not be prescribed along with other drugs with a similar effect.
- There is an increased risk of bleeding with SSRIs in those on NSAIDs and Aspirin.
- Do not prescribe an SSRI with warfarin and heparin due to antiplatelet effect.
- There is a risk of cardiac arrhythmias with high dose venlafaxine and possible exacerbation of hypertension with venlafaxine and duloxetine, hence the need to monitor blood pressure.
- When prescribing lithium, be careful about the brand due to bioavailability differences. Arrange for ECG, TFT, and U&E before initiation, and TFT and U&E every 6 months thereafter; and more often if there is renal impairment.
- Dementia, cardiovascular problems, diabetes and Parkinson's disease, commonly found in the elderly can worsen with highly anticholinergic drugs.
- SSRIs such as fluoxetine, paroxetine, and fluvoxamine have higher risks of drug-drug interactions.
- There is an increased risk of hyponatremia with antidepressants, especially SSRIs. Due to reduced renal functioning with ageing, hyponatremia secondary to a syndrome of inappropriate antidiuretic hormone secretion (SIADH) is an ongoing risk. Patients taking antidepressants, particularly SSRIs and venlafaxine, are affected.
- If a second antidepressant is added, and if both are serotoninergic, monitor for the emergence of Serotonin Syndrome.
- Beware of discontinuation syndrome for SSRIs and SNRIs This can be prevented by gradual tapering of the antidepressant.
- Exercise particular caution in switching from fluoxetine to other antidepressants; because fluoxetine has a long half-life.
- Mirtazapine can cause bone marrow suppression.

Alcohol and antidepressants

Alcohol can make depression worse and can also increase the side effects of antidepressants, such as drowsiness, dizziness, and co-ordination problems. Hence it is generally advised to avoid alcohol while taking antidepressants.[6] Interaction of SSRI and related antidepressants with alcohol resulting in serious risk of pathological intoxication with gross disinhibition, violence, and memory impairment has also been reported though not specifically among older adults.[19]

Electro Convulsive Therapy (ECT) and other somatic treatments

ECT is considered when the treatment response required is rapid. Severe depression, psychotic features, catatonic symptoms, high risk of suicide, refusal of food, unable to take medications, treatment resistance, past history of good response to ECT are indications for ECT. ECT is relatively contraindicated in patients with recent myocardial infarction, brain tumour, cerebral aneurysm, and uncontrolled heart failure. It is a safe treatment option with better outcomes in the elderly.[20]

There is some evidence to show higher age to be associated with higher rates of response.[21] Elderly treated with ECT have a significantly shorter time to remission than those given pharmacological treatments.[22] ECT is effective in as many as 70%–80% of elderly with major depression independent of age or any pre-existing cognitive impairment.[20] Various aspects of ECT in the elderly have been reviewed,[23] and the following suggestions are offered: Start with right unilateral electrode placement as it has lesser cognitive side effects and if no improvement shift to bilateral electrode placement. In severe depression, start with bilateral ECT. It is better to start with twice weekly; and if there is no

adequate response shift to thrice weekly; this may be associated with faster improvement but higher risk of anterograde amnesia. Six to twelve ECTs are the usual course of treatment and consider the patient to be non-responsive after 12 treatments. The elderly are more susceptible to confusion, especially with pre-existing cognitive impairment. Assess 24 hours before ECT and if confusion is a concern, change from bilateral to unilateral placement.

Alternatives to ECT, like repetitive transcranial magnetic stimulation (rTMS) and transcranial direct-current stimulation (tDCS), are useful treatment modalities with fewer side effects but require more evidence for their effectiveness. Some other somatic treatments, albeit infrequently used, include vagal nerve stimulation, deep brain stimulation light therapy, and sleep deprivation.

Monitoring during treatment

Patients who are started on antidepressants, and are not considered to be at increased risk of suicide, should be reviewed in a week or two; however if there is a risk of suicide, it is recommended that they are reviewed in a week. After that regular reviews for example, at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals, if treatment response is good are needed.[4] Factors affecting adherence to medications include attitude, expectations, side effects, and physical health status. Measures to improve treatment adherence include simplifying the medication regime, explaining what to expect, and having a proper plan and regular reviews. Response to treatment should be evaluated not only on clinical symptoms but also on the improvement of the day-to-day functioning. Although depression rating scales and percentage changes are useful, pragmatism and clinical judgment should take precedence. Patients who have had their antidepressant dose increased should be monitored for an increase in the severity of side effects or the emergence of newer side effects. It is also important at each review to monitor for any worsening of depressive symptoms, emergence of agitation or anxiety, or an increase in the risk of suicide.

Continuation, maintenance, and relapse prevention treatment

There is a high risk of relapse after a depressive episode, especially in the first 6 months, and this risk declines with time in remission.[3] Although treatment guidelines vary in their suggested duration for continuing antidepressant treatment after remission of the depressive episode, there is consensus that medication-responsive patients should have their medication continued at the acute treatment dose even after remission. Important factors affecting the risk of relapse and decision to continue antidepressants are given in Box 4 below.

NICE recommends continuation of antidepressant medication for at least 6 months after remission of an episode of depression.[4] The need for continued antidepressant treatment beyond 6 months should be based on the presence of risk factors for relapse. The depressed elderly should be advised to continue antidepressants for at least 2 years if they are at risk of relapse or if they have had two or more episodes of depression in the recent past, during which they experienced significant functional impairment. Maintenance treatment beyond 2 years should be advised for those after a thorough evaluation of clinical history, functional impairment, and risk factors. Longer duration treatment is required for those with a history of severe or prolonged episodes or if the consequences of relapse are likely to be severe.

Box 4: Factors affecting risk of relapse and decision to continue antidepressants

- Presence of residual symptoms
- Higher number of previous episodes of depression
- Longer episode duration
- More severe episodes of depression
- Functional impairment during episodes
- Higher degree of treatment resistance
- Shorter intervals between episodes of depression
- Concurrent physical health problems
- Psychosocial difficulties
- Disability, related to medical illnesses

The World Federation of Societies of Biological Psychiatry's treatment guidelines for depression also recommends that the continuation phase of treatment lasts at least 6 months following remission of acute symptomatology.[2] Treatment should be prolonged to 9 months in patients with a history of long previous episodes and should continue even longer in cases of residual symptomatology and until such symptoms have subsided and in those with psychotic depression. The British Association for Psychopharmacology advises 6 to 9 months of continued treatment after remission in patients at a lower risk of relapse, e.g. first episode without other risk factors and to consider a treatment duration of at least 1 year in patients with an increased risk of relapse.[3] In higher-risk patients (e.g. more than five lifetime episodes and/or two episodes in the last few years), treatment for at least 2 years if not longer-term treatment should be considered. Consider long-term treatment in the elderly as this reduces the risk of relapse by half. A pragmatic approach would be to actively involve the patient in the decision making process with regular monitoring of mental status, side effects, risk factors, physical health, and psychosocial well-being. It is always important to clarify that long-term antidepressant treatment reduces the risk of relapse and that antidepressants are not addictive, thereby supporting and encouraging patients, who have benefited from being on an antidepressant, to continue it. Discuss about advanced decisions and advanced statements in those with a history of severe depression, especially if treated under the Mental Health Act.

Psychological Interventions

Psychological interventions such as Cognitive Behavioural Therapy (CBT), Inter-Personal Therapy (IPT), and Problem Solving Therapy (PST) are all equally effective in older and younger adults with depression.[24,25] However, CBT has the most substantial evidence in support of its effectiveness. The influence of physical diseases, frailty, and cognitive impairment on the efficacy or feasibility of psychotherapy has not been assessed in high-quality studies.[1] People with depression have negative automatic thoughts arising from dysfunctional beliefs. CBT aims to identify and modify these thoughts, thereby bringing about a change in their mood and behaviour. In the elderly, cognitions associated with physical health, role changes, losses, and transitions might have added significance. Adaptations suggested in the elderly with cognitive slowing include presenting information slowly with frequent repetitions and summaries, presenting information in alternate ways and encouraging patients to take notes, and presenting new information in the context of previous experiences.[26]

IPT works on the premise that there exists a reciprocal relationship between interpersonal relationships and mood, and resolving interpersonal conflicts results in improvement of mood and vice versa. IPT views interpersonal difficulties as triggers for depression. It recognizes four categories of interpersonal difficulties associated with the onset and persistence of depression as IPT problem areas: grief, disputes, life changes, and loneliness/social isolation.[27]

Problem Solving Therapy (PST) helps people to find the best possible solution to current and everyday problems and teaches them the skills to help solve future problems. PST involves various steps such as problem orientation, problem definition, generation of solutions, evaluations of solutions, selection of the best possible solution and solution implementation, and evaluation. It uses a hands-on approach using discrete, easily taught steps to solve problems, and is very appealing and practical.[28] Individual CBT should be offered to those with depression who are considered to be at significant risk of relapse, to those if they have relapsed despite antidepressant medication and to those with residual symptoms despite treatment.

Mindfulness-based cognitive therapy can be offered to those who are currently well but have experienced three or more previous episodes of depression.[4] Psychological and behavioural treatments should be administered by appropriately trained practitioners using relevant treatment manuals.[3] Combined psychological therapy and pharmacological therapy is more effective than psychological treatment alone for older people with depression.[25]

Prognosis of late-life depression

Morbidity and mortality are increased in the depressed elderly due to medical comorbidities and poor physical health.[29] One-third of all elderly patients who are treated with an antidepressant medication achieve remission. Using a sequential treatment protocol, 96.3% achieved a response and 84% achieved complete remission within 3 years of treatment.[30,31] It was found that greater depressive symptom severity and longer duration of the depressive episode at baseline predicted poor recovery. The elderly have more medical comorbidity and more previous depressive episodes, both of which adversely affect the outcome, and the relapse rates appear higher than in younger subjects.[32] The relapse rate of depression in the elderly within two years of stopping antidepressants is as high as 60%.[33,34] Without adequate treatment, prognosis in older people is poor, and they have a higher relapse rate than their younger counterparts.[1] Furthermore, there is a high risk of depressive relapse in the elderly with comorbid medical illnesses.[3]

Conclusion

Late-life depression is an unrecognized and undertreated condition, which results in a poor quality of life. General practitioners and non-specialists have a major role to play in identifying those with depression who present to them for physical problems and may often be reluctant to acknowledge mental health problems and seek help. Non-specialists should be sufficiently skilled in the following aspects: screening questions to ask those with suspected depression, appropriate history taking, psychiatric evaluation, and planning of the treatment. The treatment approach should be multimodal; encompassing biological, psychological, and social interventions. Special precautions should be taken when prescribing antidepressant medications in the elderly.

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