

Antidepressant treatment for depression in the elderly

There is a high risk of side effects when prescribing antidepressants in the elderly. These can be avoided or minimised by tailoring the choice of antidepressant to the individual, by being aware of potential drug interactions and by bearing in mind the impact of co-morbidities. **Drs Ayodeji Soyinka and David Lawley** explore the evidence base and main side effects of antidepressants in common use in the elderly and how these might influence prescribing.

Depression is a common symptom in later life. The average prevalence of clinically significant depressive syndrome in community dwelling older people is estimated to be 13.5 per cent¹. However, the rate of strictly defined depressive disorder in community dwelling older people using standardised diagnostic criteria such as the ICD 10² or DSM 4³ is lower, between 0.5 and three per cent⁴. The rate is higher among elderly patients in hospitals or in nursing homes⁵. It is also higher among those with chronic medical conditions such as Parkinson's disease, cardiovascular diseases, Chronic Obstructive Pulmonary Disease (COPD), dementia and stroke^{5,6,7}.

Because antidepressants are inexpensive and readily available, they tend to be prescribed for elderly people with depressive disorder. While it is good practice that elderly people are given the opportunity to benefit from what has been shown to be effective pharmacological interventions, the wide spread use of antidepressants can expose elderly people to untoward effects. This is because the elderly as a group are more prone to side effects of medications including antidepressants⁸, and they are more likely to have multiple physical pathologies and to be taking multiple medications. This increases their risk of drug–drug interactions and drug–disease interactions significantly. There may also be age related pharmacokinetic

changes affecting the absorption, protein binding, distribution, metabolism and excretion of drugs.

Despite this, not much attention is being paid to the adverse effects of antidepressants in the elderly in national guidelines, research and media attention. For instance there is only a brief reference to the elderly in the *National Institute of Health and Clinical Excellence* (NICE) guideline on the management of depression in primary and secondary care released in December 2004⁹. Elderly people over the age of 75 years are under-represented in clinical trials of antidepressants and as a result the evidence base for use in this group of people is relatively poor¹⁰⁻¹².

Since the introduction of the first tricyclic antidepressants in the late 50s, the psychopharmacology of antidepressants has developed a great deal and as a result, newer antidepressants with much improved tolerability and side effect profiles are now in routine clinical use. This is not to say that newer antidepressants are free from significant side effects. For example, gastrointestinal bleeding in elderly people can be associated with taking Selective Serotonin Reuptake Inhibitors (SSRIs)¹³. Potential side effects can, however, be avoided or minimised by tailoring the choice of antidepressant to the individual, by being aware of potential drug

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interactions and by bearing in mind the impact of co-morbidities. In this article, we explore the evidence base for effectiveness and the main side effects of antidepressants in common use in the elderly and how both these factors might influence prescribing.

Effectiveness

The efficacy and effectiveness of antidepressant treatment in depressed elderly people have been demonstrated in randomised control trials and reviews^{14,15}. Available data suggest that antidepressants are effective in 50 to 60 per cent of cases compared with a 30 per cent recovery rate on placebo⁴. The placebo response is greatest in those with mild depressive disorder and hence antidepressants are not recommended as initial treatment in those with mild depressive disorders. This is consistent with the NICE guideline⁹. All antidepressants have roughly equal efficacy, although the effectiveness may differ depending on tolerability. The general consensus is that SSRIs and other newer antidepressants are better tolerated than the tricyclics and related antidepressants. In line with this, NICE recommends that an SSRI should be first choice when an antidepressant is to be prescribed in routine care⁹. Of course, the choice of antidepressant will depend on other factors as well as including patients' preference, co-morbidity, potential side effects, risk of drug interactions, past use of antidepressants and risk of overdose as well as associated symptoms of depression such as insomnia and agitation.

In patients severely ill with depression there is a contention that tricyclic antidepressants are more effective than SSRIs but the evidence is inconclusive. Also, in some studies which were not necessarily in older people, venlafaxine has also been shown to be more effective than the SSRIs in the management of moderately severe depression⁵.

Venlafaxine at doses above 200mg/day is a recommended treatment option in the management of refractory depression¹⁶. This complies with NICE guidelines that venlafaxine should be considered in those who have failed to respond to two trials of antidepressants. It is very important to be aware that older people take longer to respond to antidepressant treatment and as a consequence are at risk of being prematurely considered non responsive. They may have their antidepressant switched when they

are yet to have an adequate trial of treatment. In order to reduce this risk, NICE recommends that in older adults antidepressant treatment should be given for a minimum of six weeks before it is considered ineffective⁹. In those who have shown partial response during the first six weeks, NICE recommends treatment for a further six weeks⁹. Maintenance treatment is recommended for those who have recovered from an episode of depression. After the first episode, the expert consensus on the treatment of depression in older patients is that treatment should continue for at least one year¹².

NICE has also recommended that patients who have experienced two or more depressive episodes in the recent past and have experienced significant functional impairment during these episodes should be advised to continue treatment for two years. This applies to both older and working age adults. Patients should be maintained on the same dose that led to remission.

Some common side effects of antidepressants

This article will now explore common antidepressant side effects that are of particular significance in the elderly person. We will look in detail at how side effects may arise and how it may influence antidepressant choice.

Postural hypotension

Lowering of blood pressure is one of the most common cardiac effects of antidepressants in the elderly. When severe, it can result in postural hypotension. Postural hypotension is partly due to the blockade of alpha-1 adrenergic receptors. The risk of postural hypotension is increased in those with left sided heart failure and in those on antihypertensive or diuretic treatment¹⁷.

The following antidepressants are associated with high to moderate risk of postural hypotension – tricyclics, monoamine oxidase inhibitors, trazodone, and nefazodone¹⁶. Lofepramine does not lower blood pressure as much as the other tricyclics, and although the risk is less, postural hypotension can occur during treatment with other antidepressants including venlafaxine, mirtazapine and the SSRIs¹⁸. Venlafaxine can also increase blood pressure especially at doses above 200mg daily thus blood pressure measurement is recommended at higher doses. Postural drop

tends to occur early in the course of treatment and since it is not dose dependent, unless a patient is on a high dose, dose reduction is unlikely to be of benefit⁶. Postural hypotension is associated with increased risk of falls and fractures. The risk can be significantly reduced by checking for a history of postural drop and by measuring standing and supine blood pressures before prescribing antidepressants that are associated with this side effect, especially tricyclics. Postural hypotension can be managed by changing to a different class of antidepressant or, if for clinical reasons this is not possible, fludrocortisone and pressure stockings can be used.

Anticholinergic side effects

These include dry mouth, constipation, urinary hesitancy, blurred vision and tachycardia. Anticholinergic side effects are particularly associated with the tricyclics because of their high affinity for the muscarinic receptor. These symptoms can have a significant impact on the quality of life of an elderly person. Many elderly people suffer from some degree of visual loss that may be due to a variety of causes such as cataract and age related macular degeneration. Antidepressant induced blurred vision can worsen visual loss and as a result can affect the elderly person's ability to manage. Loss of vision also increases the person's risk of falls and associated complications. Tricyclics and SSRIs both produce dry mouth as a side effect and this can make the use of dentures more difficult. It also increases the risk of oral infections such as candidiasis¹⁸. It is important to bear this possibility in mind especially in those who are already prescribed drugs that produce xerostomia such as diuretics. Urinary hesitancy may result in urinary retention especially in those with prostate problems. These complications can be prevented through careful choice of antidepressants and monitoring.

Cardiac side effects

Tricyclics have a quinidine like effect, in that they have type 1a anti-arrhythmic properties. As a result of this property they tend to slow cardiac conduction and can occasionally induce heart block and arrhythmia⁶. In view of this, tricyclics should be prescribed with caution in patients with pre-existing cardiovascular diseases. NICE recommends obtaining an electrocardiogram (ECG) and blood pressure measurement before prescribing a tricyclic for depressed patients at significant

risk of cardiovascular disease – many of whom would be elderly⁹. ECG changes that are clinically significant include lengthening of the PR, QRS and QT intervals⁶. Tricyclics are contraindicated after a recent myocardial infarction¹⁸.

In December 2004, following review of the safety of antidepressants, the Committee on the Safety of Medicines (CSM) recommended that venlafaxine should no longer be prescribed for patients with heart diseases, electrolyte imbalance or hypertension and that treatment with venlafaxine should be initiated only by specialist mental health practitioners including general practitioners with a special interest in mental health. The recommendation arose out of the CSM's concern that venlafaxine has been linked to incidents of sudden death and fatal overdose¹⁹. The company that manufactures venlafaxine disagrees with the CSM findings and they are challenging the recommendation.

SSRIs are generally recommended in cardiovascular diseases. Of all the SSRIs, sertraline is the one with the best evidence in this group of patients. In those with a history of acute myocardial infarction or unstable angina, sertraline has been shown to be a safe and effective antidepressant⁷.

Risk of overdose

In the management of depressed people at high risk of overdose, it is very important to avoid antidepressants that are lethal in overdose. In view of their cardiotoxicity, tricyclics are dangerous in overdose and should be avoided in patients who are suicidal. Compared with other tricyclics, lofepramine is less cardiotoxic. As highlighted above, venlafaxine has also been linked with cardiotoxicity in overdose and should also be avoided in patients who are at high risk of self harm. An Australian study also found that the SSRIs are relatively safe in overdose except citalopram, which was found to be significantly associated with QTc prolongation²⁰.

Similarly, in a two year retrospective review of consecutive patients admitted to the toxicology unit of Edinburgh Royal Infirmary, the researchers found that in comparison to venlafaxine, mirtazapine and nefazodone, citalopram was more likely to cause QT prolongation²¹. Citalopram, therefore, should be prescribed with caution in those who are at risk of taking an overdose especially those with a history of cardiovascular disease.

Table 1. Doses in the elderly

Antidepressants	Starting dose Elderly	Maximum dose	Starting dose Adults	Maximum dose
Dosulepin	50-75mg	75mg*	75mg	150mg
Trazodone	100mg	300mg	150mg	300mg
Citalopram	20mg	40mg	20mg	60mg
Fluoxetine	20mg	60mg	20mg	80mg

* (may be sufficient)

Delirium

Delirium and confusion can be induced by antidepressant treatment. These are mainly due to the anticholinergic and antihistaminic effects of the antidepressant agent hence these particular side effects are more likely to occur in those elderly patients taking tricyclics rather than other groups of antidepressants. The risk is greatest in those with an underlying dementia. Delirium can present with affective symptoms and because of this, may be confused with worsening of depression. It is very important to bear this possibility in mind especially in those patients whose depression is worsening despite adequate treatment.

Hyponatraemia and syndrome of inappropriate ADH secretion

All antidepressants have been implicated in inducing hyponatraemia although it has been reported more frequently with SSRIs. Being elderly is a recognised risk factor for antidepressant induced hyponatraemia. Other risk factors include female sex, low body weight, co-therapy with other drugs known to induce hyponatraemia (carbamazepine, diuretics, Non Steroidal Anti-Inflammatory Drugs (NSAIDs) and cancer chemotherapy), medical co-morbidities (hypothyroidism, diabetes, COPD, hypertension, head injury, stroke, various cancers) and impaired renal function¹⁶. The CSM has advised that hyponatraemia should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant¹⁸. When mild hyponatraemia can present with lethargy, which again could be misinterpreted as worsening depression and in response the antidepressant dose could be increased. This could make the hyponatraemia worse. Management of hyponatraemia involves stopping all offending drugs including antidepressants²². Mild cases can be managed by fluid restriction²¹ and daily

monitoring of sodium. Patients with serum sodium less than 125mmol/l should be referred for specialist medical care¹⁶.

Upper gastrointestinal bleed

Antidepressants have also been linked with a variety of abnormal bleeding conditions including gastrointestinal bleeding^{13, 23, 24, 25}. The results of some studies suggest that the risk of abnormal bleeding correlates with the degree of serotonin reuptake inhibition by the antidepressant^{23, 24}. The biological basis for this is that serotonin is involved in platelet aggregation thus agents that prevent reuptake may reduce platelet serotonin stores and as a consequence impair platelet function. SSRIs have been shown to increase the risk of gastrointestinal bleed in the elderly^{13, 25}. It is important to consider this when prescribing SSRIs and other serotonergic antidepressants for elderly people. The risk of abnormal bleeding may be higher in those over the age of 80 years, those with previous history of gastrointestinal bleed or those on NSAIDs and aspirin.

Mirtazapine can cause reversible agranulocytosis. People prescribed mirtazapine should be informed of this risk and advised to report any fever, sore throat or other signs of infection during treatment¹⁸. Blood count monitoring is also recommended.

Sexual dysfunction

Sexual dysfunction such as arousal problems, reduced libido, delayed orgasm and impaired ejaculation are recognised side effects associated with all classes of antidepressants. Some antidepressants are considered to be less likely to cause sexual dysfunction. There is however insufficient evidence in the literature to support this claim. One systematic review

found that available evidence was insufficient to justify claims of differences in the propensities of antidepressants to cause sexual dysfunction²⁶. Sexual side effects are often not reported but it is necessary to consider them when discussing the risk and benefit of a particular antidepressant. Trazodone, for example, can rarely cause priapism.

Akathisia

Akathisia is an extrapyramidal side effect that is most often associated with typical antipsychotic medications but can also be caused by antidepressants. It is characterised by difficulty staying still and an intense feeling of inner restlessness. There is some evidence in support of the view that akathisia induces suicidal behaviour²⁷. Bearing this in mind, clinicians are advised by NICE to actively seek out signs of akathisia especially in the early stages of treatment.

Akathisia can be difficult to diagnose, hence a high index of suspicion is needed. It is managed by withdrawing the offending drug or by reducing the dose if this is possible. Where dose reduction is not possible, the patient can be treated with a beta-blocker such as propranolol and if this is ineffective then a benzodiazepine such as diazepam or clonazepam could be used²⁸.

Some patient characteristics of significance in the elderly

Agitated and anxious patients

Tricyclic antidepressants could be considered as possible alternatives to SSRIs in situations where sedation is required, though this must be balanced against the risk of side effects due to anticholinergic effects or cardiotoxicity. An alternative approach would be to prescribe sedatives, such as short acting benzodiazepines for a limited period of time, as an adjunct to the SSRI. In psychotic depression, antipsychotic drugs should be added to the antidepressant, in order to fulfil the dual role of sedation.

Dementia

A recent Cochrane review revealed that this is a poorly researched area and as such there is not much evidence supporting the efficacy of antidepressants in people with dementia²⁹.

Antidepressants with strong anticholinergic properties such as the tricyclics might worsen confusion and are best avoided. In clinical practice, SSRIs are usually prescribed when treating depression in people with dementia. Where a person with dementia has difficulty adhering to treatment, an antidepressant with a long half life such as fluoxetine could be prescribed as it could be taken every other day. Furthermore, omitting doses through forgetfulness is unlikely to precipitate withdrawal symptoms.

Parkinson's disease

Parkinson's disease is a disease of later life, and 40 to 50 per cent of people with Parkinson's disease will experience co-morbid depression³⁰. The treatment of Parkinson's disease involves the use of combinations of drugs with potential risk of drug interaction. Therefore, prescribing an antidepressant for co-morbid depression could further increase this risk. Tricyclics and SSRIs are effective pharmacotherapy for depression in Parkinson's disease but there are some concerns related to side effects. Tricyclics, for instance, may worsen cognitive function, cause orthostatic hypotension or induce delusions³⁰.

There is also debate that SSRIs may worsen parkinsonism. On the positive side, tricyclics might help extrapyramidal symptoms due to their anticholinergic effects³¹. Given their favourable side effect profiles and reduced drug interactions, SSRIs are recommended, particularly those with neutral or weak dopaminergic effects such as sertraline and citalopram. SSRIs should not be prescribed for patients on selegiline (a monoamine oxidase-B inhibitor) because of increased risk of serotonin syndrome¹⁸.

Dose reduction

Despite the advancement in psychopharmacology, the adage 'start low and go slow' is advocated when prescribing antidepressants in elderly people. In working age adults, most new antidepressants can be started at their therapeutic dose without the need for dose titration. In the elderly dose titration is often done in an effort to reduce the risk of side effects. When dose titration is carried out, it is important that the therapeutic dose is achieved where tolerable although there are studies suggesting that elderly people may respond to lower doses of antidepressant. For some antidepressants, the manufacturers have

Key points

- > Older people are at a high risk of side effects and drug interactions.
- > Antidepressants used should be chosen carefully in order to reduce this risk.
- > SSRIs are recommended as first line antidepressant in routine care.
- > Antidepressants should be tailored to the individual patient taking into consideration the potential for drug interaction, the effect of physical co-morbidity and most importantly the patient's previous history of antidepressant use.
- > Older people take longer to respond and should be treated for longer before they are considered non responsive.

recommended a reduced initial dose and a lower final dose in the elderly person¹⁸.

Discontinuation syndrome

Discontinuation syndrome may occur following abrupt cessation of antidepressant treatment. Patients often report dizziness, nausea, vomiting, flu like symptoms, fatigue, anxiety and irritability. These symptoms are usually self limiting but on occasions can be severe. All patients prescribed antidepressants must be informed of the risk of discontinuation syndrome⁹.

Discontinuation syndrome is more likely with antidepressants with short half lives, such as paroxetine. Fluoxetine, an antidepressant with a long half life, is recommended as a means of managing withdrawal symptoms in those patients who have had difficulty in stopping treatment. Also, when an antidepressant is to be stopped, this should be done by gradual dose reduction over a number of weeks.

Conclusion

SSRIs are currently the drugs of first choice in the treatment of moderate to severe depression in the elderly because of their more favourable side effect profiles and lower risk of drug interaction. However, it is important to select antidepressants depending on the individual patient symptoms and characteristics.

As a general rule, polypharmacy should be avoided and older people may need more frequent monitoring and slower dose titration than their

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younger counterparts. There is also mounting evidence to support the use of psychological therapies such as cognitive behavioural therapy in older people.³² ■ GM

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Antidepressants are effective in treating depression in the face of medical illnesses, although caution is required so that antidepressant therapy does not worsen the medical condition or cause adverse events.[17] For example, dementia, cardiovascular problems, diabetes, and Parkinson disease, which are common in the elderly, can worsen with highly anticholinergic drugs.[18]. Nonetheless, atypical antipsychotics may prove to be an effective treatment for severe or refractory depression in the elderly who fail to respond fully to other medications. Atypical antipsychotics at the lowest doses for symptom control are also recommended for the treatment of psychotic symptoms associated with depression. Tricyclic antidepressants were once prescribed for the elderly, but are now not considered first line treatment agents for the elderly. The side effects and potential for drug interactions are considered too high to be safe in most cases for elderly patients. The major side effects that can happen include: Postural hypertension, which contributes to fractures and falls. Electroconvulsive therapy, also known as electroshock, is a controversial treatment for depression in elderly adults. It has been shown to have severe side effects in some cases, such as memory loss. This should only be considered as a treatment if other options have proven ineffective for your depression. This review compared the efficacy, withdrawal rates and side effects of different antidepressant classes in the treatment of depression in older people. Thirty-two studies provided data for the review. Our main findings indicate that tricyclic antidepressants (classical and tricyclic related) and selective serotonin reuptake inhibitors (SSRIs) are equally efficacious. However, when comparing the two tricyclic groups with SSRIs we found that tricyclic related antidepressants were similar to SSRIs in terms of overall withdrawal rate, and classical tricyclic antidepressants were associated with a... Antidepressants for depressed elderly. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No. Antidepressants are a popular treatment choice for depression. Although antidepressants may not cure depression, they can reduce symptoms. The first antidepressant you try may work fine. But if it doesn't relieve your symptoms or it causes side effects that bother you, you may need to try another. So don't give up. A number of antidepressants are available, and chances are you'll be able to find one that works well for you. And sometimes a combination of medications may be an option. Also, if an antidepressant has been effective for your depression in the past, it may work well again. Interaction with other medications. Some antidepressants can cause dangerous reactions when taken with other medications. Pregnancy or breast-feeding.