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Contemporary Therapies for Depression in Older People

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ABSTRACT

Major depressive disorder is common in the elderly and is associated with significant morbidity and disability, as well as increased risk of mortality. Extensive literature is extant examining the efficacy and tolerability of the earlier antidepressants but there are comparatively fewer trials examining the newer antidepressants, the so-called 'third generation' antidepressants with a variable mode of action. This article reviews the literature published in the past 10 years on the efficacy and tolerability of the new antidepressants – escitalopram, venlafaxine, duloxetine and mirtazapine – used in treating depression of old age. There are no published data for the newly released desvenlafaxine in the elderly population. Due to the limited number of published trials and their highly heterogeneous nature, specific treatment recommendations for depression in older people are not supported by solid empirical evidence. Clearly, further studies on the management of depression in older people are needed in order to develop reliable and practical guidelines.

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INTRODUCTION

Major depressive disorder is common in the elderly and is associated with significant morbidity and disability, as well as increased risk of mortality. The estimated prevalence of major depression in people over 65 years of age varies widely and ranges from 1.6 to 27%, dependent on the population studied, sample size, definition of depression and method of diagnosis.¹ The estimated prevalence does not include older adults who have clinically significant depressive symptoms not meeting criteria for major depressive disorder, estimated to be around 10 to 15%. This prevalence estimate does not include the 25% of patients over 65 years of age with a chronic medical illness who experience depressive symptoms.^{2,3}

Depression in older people is often inadequately managed, due to a combination of factors, such as under-diagnosis and overly cautious use of medications.⁴⁻⁶ Along with these issues, the specific complex factors associated with old age, such as the presence of multiple comorbidities, physical disability and polypharmacy, impact on the effective treatment of depression.⁷ Independent of physical problems, depression in the elderly is slower to respond to treatment than younger

individuals.⁸ Frequently, there is only partial response to treatment and in some cases non-response, which adds an increased level of complexity in the management of older people with depression.⁹

There is extensive literature examining the efficacy and tolerability of the first-generation antidepressants (tricyclic antidepressants and monoamine oxidase inhibitors), as well as the second-generation antidepressants (selective serotonin reuptake inhibitors), in older people. However, there are comparatively few trials examining the new antidepressants, the so-called 'third-generation' antidepressants with a variable mode of action. The third-generation antidepressants include venlafaxine and mirtazapine (available for 10 to 15 years), duloxetine (released in Australia in the past 12 months) and desvenlafaxine (recently released in Australia and overseas). Escitalopram, an isomeric form of citalopram, has been in clinical use for the last 10 years, and has the theoretical benefit of improved tolerability compared to citalopram. This article reviews the literature published in the past 10 years on the efficacy and tolerability of the new antidepressants in treating depression of old age.

CLINICAL FEATURES OF DEPRESSION IN OLD AGE

Depression in older people can be conceptualised as being either early onset, with the initial episode occurring before 65 years of age, or late onset, beginning after 65 years of age. Early-onset depression is more often associated with a family history of mood disorders suggesting that genetic vulnerability is less relevant in the late-onset group. Older people with early-onset depression are more likely to have had a higher number of episodes, which may contribute to a poorer prognosis compared to patients with late-onset depression.¹⁰

Depression often has an atypical presentation in older people. Many researchers have observed that older people are less likely to report feelings of sadness, or identify with the term 'depression'. This can be due to a lack of prior experience or knowledge of the illness, or the acceptance by some older people that feeling sad is a normal part of ageing. Common presenting complaints may instead include anxiety, somatic complaints and memory loss. Psychotic and melancholic symptoms are more common in elderly patients; psychotic symptoms occur in 20 to 45% of hospitalised depressed patients.^{4,10} Psychotic symptoms usually include mood-congruent delusional beliefs with themes of persecution, nihilism, guilt and somatic complaints.

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Suicide rates in patients older than 65 years of age range from 5 to 20% of all suicides.^{4,10} Suicidality can affect treatment response and remission, with slower response to treatment and higher rates of relapse in suicidal patients.⁹ Rates of suicide are higher in older men than older women, in divorced or single older people, and in widowers compared to widows.¹¹ Acts of deliberate self-harm in older patients should be managed as a 'failed suicide', however trivial the attempt, as most incidents of self-harm in older persons are carried out with high suicidal intent.¹¹

GRIEF VERSUS DEPRESSION

It is important to distinguish normal grief and grieving from major depression. Older people experience many losses as they age, such as their spouse, lifelong friends, family and loved ones. However, losses may also include loss of independence, physical health, cognitive ability or financial security. Grieving is the normal process of adjustment to such losses allowing people to come to terms with life changes and continue with a new perspective. When grief is prolonged, or associated with symptoms of anhedonia, loss of meaning, or morbid preoccupation with the lost person (or function), depression should be considered as a diagnosis.

MEDICAL ILLNESS

Medical illness is often associated with high rates of depression, and medical burden also impacts negatively on treatment response.⁹ The link between depression and cardiovascular disorders is well established, and there is evidence for higher rates of depression in patients with cancer and neurological disease, especially stroke, Alzheimer's disease and Parkinson's disease.¹⁰ Medical illness can also mask the symptoms of depression and add to the difficulties of diagnosis. Conversely, depression can worsen the course of comorbid medical illness, and is a risk factor for increased morbidity and functional disability, as well as a risk factor for mortality in medically hospitalised and nursing home patients.^{5,7,10} Many medications used in the elderly are associated with precipitating or exacerbating depression.^{11,12} For example, systemic corticosteroids, antihypertensives (e.g. beta-blockers, calcium channel blockers), anti-parkinsonian medications, analgesics, benzodiazepines, cytotoxic drugs and radiotherapy.¹¹⁻¹³

Cerebrovascular Changes

Cerebrovascular changes are common in the ageing brain, and there is a well-known association between vascular risk factors and depression. Cerebrovascular incidents predispose older patients to late-onset depression.¹⁴ Depression occurs in approximately 25% of all stroke survivors.^{4,10} Additionally, cerebrovascular changes that occur in the context of ageing and vascular risk factors, but without physical sequelae, are also related to depression. The severity of cerebrovascular changes, especially subcortical white matter hyper-intensities, are linked to the presence of depressive symptoms and a history of late-onset depression.¹⁵ A poor outcome in older depressed patients has been associated with the severity of white matter changes.¹⁶

COGNITIVE IMPAIRMENT

An increased rate of cognitive and executive dysfunction has been noted in patients with late-onset depression and cognitive deficits often persist even after the depression has resolved.⁴ There is growing epidemiological evidence that depression is a risk factor for patients developing cognitive impairment or dementia later on in life.¹¹ The underlying mechanism is unclear, but may include factors such as the reported association between chronic depression and hippocampal atrophy in older people, or the adoption of unhealthy lifestyles by depressed patients which compound risk factors for vascular disease and dementia.¹¹ As yet, there is no precise method for predicting which patients will develop lasting cognitive impairment.

TREATMENT ISSUES

Response

Approximately 40 to 50% of older people with non-psychotic major depressive disorder respond to a first trial of an antidepressant. Of those who do not respond, 50% may respond when either switched to an alternative antidepressant or if the dose of the original antidepressant is augmented.⁹ The remainder of older people tend to follow a chronic, treatment-resistant course with limited response to most antidepressants.

Several factors influence response to treatment, including severity of illness and recurrence of episodes, medical burden, comorbid anxiety, cognitive impairment and very old age (> 85 years). These factors often coexist and contribute to a slow rate of response to antidepressants and are associated with high rates of relapse and recurrence. Additionally, altered pharmacokinetic and pharmacodynamic factors, polypharmacy and reduced compensatory mechanisms contribute to variability in treatment response in older people.

Adverse Effects

Adverse effects of antidepressants also influence outcome and response to treatment, mostly in terms of compliance with therapy, but also due to exacerbation of physical illness. For example, the tricyclic antidepressants can exacerbate cardiac disease due to their adverse effects of postural hypotension and arrhythmia. The new antidepressants have less anticholinergic and anti-adrenergic properties and have low rates of cardiovascular complications. The new antidepressants have different adverse effects that may exacerbate physical illness in other ways, such as the selective serotonin reuptake inhibitors and gastrointestinal side effects resulting in (usually temporary) symptoms of nausea, vomiting and diarrhoea. In patients with multiple medical comorbidities, distinguishing between symptoms of the pre-existing illness and adverse effects of the antidepressants is important, although this can often be difficult.

Efficacy

The studies included in a review published by the Cochrane Collaboration of randomised placebo controlled trials of antidepressant use in the depressed elderly were conducted from 1984 to 1995 and included evidence from trials on selective serotonin reuptake inhibitors, tricyclic antidepressants and monoamine

oxidase inhibitors.¹⁷ The main conclusions were that all three classes of antidepressants were equally effective in the treatment of older people with depression, and that four weeks of treatment with antidepressant was likely to have a beneficial effect compared with placebo. The review also found that antidepressant treatment is effective for physically ill patients in hospital and nursing homes, despite the relative under-treatment of these patients, and that low-dose tricyclic antidepressants may be superior to placebo in physically ill inpatients. ‘Low-dose tricyclic antidepressants’ was not specifically defined but the doses used were lofepramine 70 mg and doxepin 10 to 20 mg. The authors did caution on the generalisability of these findings. This is a reissue of the original review, not an update, and therefore does not include any placebo controlled trials conducted with the new antidepressants.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The selective serotonin reuptake inhibitors introduced in the late 1980s are the most prescribed medications for depression in all age groups and are the first-line antidepressant in older patients. The selective serotonin reuptake inhibitors have long superseded the tricyclic antidepressants, despite having a similar efficacy, due to their better tolerability and safety profile.

Despite their relative tolerability and safety, selective serotonin reuptake inhibitors are not without adverse effects. Increasing evidence has emerged over the past decade on the association of selective serotonin reuptake inhibitors with a range of previously unrecognised adverse effects in the elderly.¹⁸ Some important adverse effects include hyponatraemia, increased risk of falls, platelet dysfunction and increased bleeding tendency.

Adverse Effects

Hyponatraemia

Hyponatraemia associated with selective serotonin reuptake inhibitor use is presumably caused by the syndrome of inappropriate antidiuretic hormone secretion, but the exact incidence and risk is unclear. Hyponatraemia usually develops within the first weeks of treatment but can occur at any time. This unpredictability has resulted in some authors recommending the active monitoring of sodium levels in patients prescribed selective serotonin reuptake inhibitors, with measurements taken before and after starting treatment, followed by ongoing monitoring.^{18,19}

Falls

Community-based and residential studies have demonstrated that selective serotonin reuptake inhibitors are associated with a risk of falls similar to tricyclic antidepressants; the exact cause is unknown.¹⁸

Bleeding

Selective serotonin reuptake inhibitors are also associated with increased bleeding tendency, which is believed to be due to depletion of serotonin stores in platelets. History of gastrointestinal bleeds and peptic ulcer disease may increase the risk of gastrointestinal bleeding with selective serotonin reuptake inhibitor therapy, and co-administration of warfarin with selective serotonin reuptake inhibitors has been found to increase the risk of lower gastrointestinal bleeding.¹⁸

Fractures

There is growing evidence to suggest that independent of functional or cognitive impairment, or level of associated depression, selective serotonin reuptake inhibitors are associated with hip fractures. Schneeweiss and Wang²⁰ investigated the effect of confounding bias in claims database studies (which have previously been used to assess the association between selective serotonin reuptake inhibitors and hip fractures) and found after appropriate correction for bias (RR 1.8; 95%CI 1.5–2.1).²⁰ Other studies have also found an increased risk of fractures with selective serotonin reuptake inhibitors, notably the risk appears to be greatest with prolonged use rather than early in treatment.^{21,22}

Escitalopram

The theoretical benefits of escitalopram when compared with other selective serotonin reuptake inhibitors are its lack of secondary pharmacological properties and potential for improved tolerability (although there are no head-to-head trials comparing escitalopram with other selective serotonin reuptake inhibitors in the elderly). Three studies were found examining the use of escitalopram in the treatment of depressed patients over the age of 60 years (Table 1).

Gorwood et al.²³ conducted a relapse prevention study assessing time to relapse and rates of relapse with escitalopram compared to placebo. Relapse was examined with a double-blind randomised control phase conducted over 24 weeks, following on from an open-label period of treatment with escitalopram over 12 weeks. The major

Table 1. Evaluation of escitalopram used for the treatment of depression in the elderly

Author	No. of subjects	Age (years)	Study design	Study length	Primary outcome measures	Results
Gorwood et al. ²³	305	64-91	Relapse prevention study, open-label treatment followed by DBRPCT (10-20 mg)	12 weeks (open-label) 24 weeks (DBRPCT)	Time to relapse from start of DBRPCT period. MADRS	Statistically significant benefit in prevention of relapse with escitalopram compared to placebo.
Saghafi et al. ²⁴	175	> 60	Open-label (10 mg)	6 weeks	HAM-D17 (full vs partial vs non-response)	Statistically significant difference in baseline self-esteem and anxiety in non-responders.
Bose et al. ²⁵	267	> 60	DBRPCT (10-20 mg)	12 weeks	MADRS	No significant difference in efficacy or tolerability compared with placebo.

DBRPCT = double-blind randomised placebo-controlled trial. MADRS = Montgomery-Asberg Depression Rating Scale. HAM-D17 = Hamilton Rating Scale for Depression, 17 item.

finding of this study was that escitalopram was four times more effective at preventing relapse than placebo over six months. The authors also concluded that escitalopram was well tolerated in the study population, as reflected in the low rate of withdrawals due to adverse events (13%) in the open-label period and a comparable rate of adverse events to placebo in the randomised period.

Saghafi et al.²⁴ conducted an open-label trial of escitalopram with the aim of predicting factors which would determine partial or non-response in the elderly population, a frequent issue in the management of late-onset depression. The authors concluded that low self-esteem and high baseline anxiety were significant factors in patients who did not respond to escitalopram (representing around 25% of the study population). The trial duration was six weeks, which given the often delayed onset of effect in the elderly population, was too short to effectively determine variability of response.

Bose et al.²⁵ conducted a double-blind, randomised placebo controlled trial over 12 weeks with escitalopram in patients older than 60 years. Although escitalopram was well tolerated, no significant benefit in efficacy over placebo was reported, with no significant difference in rates of withdrawal due to adverse events.

SEROTONIN AND NORADRENALINE REUPTAKE INHIBITORS

Venlafaxine

Venlafaxine is regarded as a 'dual action' antidepressant. At low doses venlafaxine inhibits the serotonin transporter, while at high doses it inhibits the noradrenaline transporter and also has a weak effect on the dopamine transporter. Similar to the selective serotonin reuptake inhibitors, venlafaxine has no α_1 , cholinergic or histamine blocking properties, and therefore a superior tolerability profile compared to tricyclic antidepressants. Use of venlafaxine is well established in adults and is becoming increasingly

recognised as a safe and efficacious treatment for older patients with major depressive disorder. The most recently published data on the use of venlafaxine in treating old age depression includes two trials comparing venlafaxine with nortriptyline, three trials comparing venlafaxine with selective serotonin reuptake inhibitors and a final trial evaluating venlafaxine in patients with dementia and depression (Table 2).

Both trials comparing venlafaxine with nortriptyline included blinding of raters and randomisation and were conducted over a three to six month treatment period. Patients with either comorbid physical illness or psychotic features were included. No differences were reported between comparators in either trial in measures of efficacy.^{26,27} The first of these trials reported that venlafaxine had a significantly more benign autonomic adverse effect profile than nortriptyline, whereas the other study found that patients treated with venlafaxine experienced significantly less anticholinergic-like adverse effects than those on nortriptyline.^{26,27}

Of the three trials comparing venlafaxine to selective serotonin reuptake inhibitors, two were large, multicentre, double-blind, randomised trials (one trial compared citalopram and the other fluoxetine and placebo).^{28,29} The third trial was also blinded and randomised, and used sertraline as a comparator. This trial had a much smaller study population and a third of the participants discontinued due to adverse events.³⁰ All three trials found equal efficacy between treatments.

The trial comparing venlafaxine to citalopram found a non-statistically significant trend towards higher rates of spontaneously reported adverse effects with venlafaxine than with citalopram. The trial comparing venlafaxine with fluoxetine and placebo, found a statistically significant increase in rates of discontinuation due to adverse effects with venlafaxine compared to placebo. Non-statistically significant rates of discontinuation were found when venlafaxine was compared with fluoxetine, although there was a trend

Table 2. Evaluation of venlafaxine used for the treatment of depression in the elderly

Author	No. of subjects	Age (years)	Study design	Study length	Primary outcome measures	Results
Gasto` et al. ²⁶	68	> 65	Single-blind RCT venlafaxine XR 225-300 mg vs nortriptyline 50-100 mg	24 weeks	HAM-D17	No statistically significant difference in efficacy or tolerability.
Kok et al. ²⁷	81	> 60	DBRCT venlafaxine XR 75-375 mg vs nortriptyline 25-200 mg	12 weeks	MADRS	No statistically significant difference in efficacy or tolerability.
Allard et al. ²⁸	148	64-89	DBRCT venlafaxine XR 37.5-150 mg vs citalopram 10-30 mg	26 weeks	MADRS	No statistically significant difference in efficacy or tolerability.
Schatzberg et al. ²⁹	300	> 65	DBRPCT venlafaxine IR 37.5-225 mg vs fluoxetine 20-60 mg vs placebo	8 weeks	HAM-D21	No statistically significant difference in efficacy (all groups). Statistically significant difference between venlafaxine and placebo in tolerability.
Oslin et al. ³⁰	52	61-99	DBRCT venlafaxine IR 18.75-150 mg vs sertraline 25-100 mg	10 weeks	HAM-D21	No statistically significant difference in efficacy. Sertraline better tolerated than venlafaxine.
Cunha et al. ³¹	31	> 60	DBRPCT venlafaxine IR 18.75-131.25 mg	6 weeks	MADRS	No statistically significant difference in efficacy or tolerability compared with placebo.

RCT = randomised controlled trial. DBRCT = double-blind randomised controlled trial. DBRPCT = double-blind randomised placebo-controlled trial. HAM-D17 = Hamilton Rating Scale for Depression, 17 item. HAM-D21 = Hamilton Rating Scale for Depression, 21 item. MADRS = Montgomery-Asberg Depression Rating Scale.

towards higher rates of discontinuation with venlafaxine. This study used the immediate-release formulation of venlafaxine, which has since been superseded by the extended release form due to gastric irritability associated with the immediate-release form, which may explain the trend towards higher rates of adverse effects in this trial.

The trial comparing sertraline with venlafaxine was conducted in nursing home residents and included patients with dementia and comorbid medical conditions. This trial also used the immediate-release form of venlafaxine. Due to the small sample size the authors were unable to make any robust conclusions about tolerability, although they did note that the venlafaxine group had higher rates of discontinuation than the sertraline group due to adverse events (which was statistically significant; $p < 0.005$). Based on this finding, the authors concluded that venlafaxine may be less tolerable than sertraline in frail nursing home patients.

The final venlafaxine study was a placebo-controlled double-blind, randomised treatment of depression in patients with dementia, using immediate-release venlafaxine.³¹ The authors found no significant difference in efficacy between the groups, but also no significant difference in reports of adverse events. There are very few randomised controlled trials on the use of antidepressants in dementia (and no other trials using venlafaxine specifically). Elderly patients with dementia are often excluded from clinical trials due to difficulties in interpreting efficacy and safety assessments. While this trial reported no benefit of venlafaxine versus placebo in treatment of patients with dementia and depression, it was limited by the brief study duration, small sample size and a low dose range of venlafaxine.

Duloxetine

Duloxetine is the second reuptake inhibitor of serotonin and noradrenaline to become available in Australia. Duloxetine has recently had Therapeutics Good Administration approval, although it has been available overseas for several years. Duloxetine's efficacy and tolerability in the treatment of major depressive disorder has been well established in randomised, double-blind, placebo controlled trials in adult patients. There are

emerging data on the use of duloxetine in the elderly for major depressive disorder, and five studies evaluating its efficacy and safety in the elderly have been published (Table 3). In addition to its antidepressant effects, there is evidence that duloxetine has efficacy in the treatment of chronic pain.

Of the five published studies, only two are double-blind placebo-controlled trials. In the first of these trials, data from a subset of patients aged 55 years and over were reported from a collection of much larger trials.³² The other was an eight week study conducted in 311 participants, and examined efficacy for cognition and chronic pain as well as depression.³³ The outcome of 'cognition' was measured by a protocol specified composite cognitive score, based on four cognitive tests (verbal learning, recall, sequencing or frontal executive function).³³ Both trials found that there was significant improvement with duloxetine in all measures of efficacy for depression compared with placebo. Furthermore, there was significant improvement in measures of back pain as well as significantly improved composite measures of cognitive performance compared with placebo, specifically in the domains of verbal learning and recall.³³ In these two studies, there were inconsistent findings for discontinuation rates with duloxetine.

An open-label evaluation was based on a subset of patients aged over 65 years taken from a 52 week study of patients aged 18 years and older.³⁴ Duloxetine was shown to have statistically significant efficacy in all outcome measures compared with baseline measurements, but a quarter of the patients withdrew due to adverse events. The most common adverse events included somnolence, dizziness, diarrhoea, hypertension and vomiting. A second open-label trial examined the efficacy of duloxetine as a second-line antidepressant in the treatment of late-life depression after failure of selective serotonin reuptake inhibitor (escitalopram) treatment.³⁵ This was a relatively small trial with only 40 patients and the measures of efficacy were recorded as level of response. The researchers found that 50% of the participants who had failed to respond to escitalopram responded to duloxetine, and 18% showed partial response. The third trial was a 12 week pilot study of

Table 3. Evaluation of duloxetine used for the treatment of depression in the elderly

Author	No. of subjects	Age (years)	Study design	Study length	Primary outcome measure	Results
Nelson et al. ³²	90	55-75	DBRPCT (60-120 mg)	8-9 weeks	HAMD-17	Statistically significant benefit in efficacy compared with placebo. Statistically significant discontinuation rates with duloxetine.
Raskin et al. ³³	311	65-90	DBRPCT (60 mg)	8 weeks	GDS	Statistically significant benefit in efficacy compared with placebo. No difference in tolerability.
Wohleisch et al. ³⁴	101	65-87	Open-label (80-120 mg)	52 weeks	CGI-S	Response: 89.4% Remission: 72.3% Discontinuation: 27%
Karp et al. ³⁵	40	> 65	Open-label 'rescue' (60-120 mg)	16.5 weeks	HAM-D17	Response: 50% Partial-response: 17.5% Non-response: 32.5% Discontinuation: 12.5%
Karp et al. ³⁶	30	> 60	Open-label pilot (60-120 mg)	12 weeks	MADRS	Remission: 46.7% Discontinuation: 6.6%

DBRPCT = double-blind randomised placebo- controlled trial. HAM-D17 = Hamilton Rating Scale for Depression, 17 item. GDS = global disability score. CGI-S = clinical global impression, severity, scale. MADRS = Montgomery-Asberg Depression Rating Scale.

Table 4. Evaluation of mirtazapine used for the treatment of depression in the elderly

Author	No. of subjects	Age (years)	Study design (dose)	Study length	Primary outcome measures	Results
Nelson et al. ³⁷	50	85-98	Open-label (15-45 mg)	12 weeks	CGI-I*	Response: 55% Well tolerated.
Schatzberg et al. ⁴⁰	246	>65	DBRCT mirtazapine 15-45 mg vs paroxetine 10-40 mg	8 weeks	HAM-D 17	Statistically significant higher rate of response at day 14 and remission at day 42 with mirtazapine. Faster decrease in mean HAM-D scores. Mirtazapine better tolerated than paroxetine.

CGI-I = clinical global impression, improvement, scale. DBRCT = double-blind randomised controlled trial. HAM-D 17 = Hamilton Depression Rating Scale, 17 item.

duloxetine examining efficacy for depression and chronic lower back pain.³⁶ All of the patients who met criteria for depression remission (47%) met criteria for pain response, and all of the patients who experienced remission sustained their improvement by week 12 (93% of subjects met criteria for pain response, and of these, 50% also met criteria for depression response). The study does not report specifically on pain response without depression response, from the data presented one might assume that this occurred in the other 50% of the 93% who experienced pain response. Safety data were not reported in this trial.

Mirtazapine

Mirtazapine is a putative dual-acting antidepressant with unique pharmacological properties. Mirtazapine increases serotonin and noradrenaline neurotransmission via interactions with presynaptic α_2 -receptors as well as postsynaptic serotonergic receptors. Two trials were found examining the use of mirtazapine in the elderly (Table 4).

A naturalistic open-label trial examined the use of mirtazapine in elderly nursing home residents.³⁷ It was a secondary analysis of a subgroup of nursing home residents older than 85 years of age from a larger trial which included a broader age range of this patient group (older than 70 years). The trial was small with only 50 participants, and included patients with dementia and comorbid medical conditions. The authors concluded that 55% of the participants responded to mirtazapine, despite the authors being unable to comment on statistical significance due to the small sample size and the study design. Due to the size and design of the study, it is difficult to draw any conclusions as to the role of mirtazapine in managing depression in the elderly population. The study was included in this review due to the limited number of studies conducted with mirtazapine in the elderly, and also due to the sample population used in this study.

The very elderly (older than 85 years) are under-represented in clinical trials.³⁸ Similarly, patients who reside in nursing homes, and who have dementia and medical comorbidities are also generally excluded from clinical trials. This population has high rates of depression (prevalence rates are 3 to 5 times higher than in older community-dwelling patients) that is generally under recognised and under-treated, resulting in a lack of clinical evidence guiding treatment for these patients.^{38,39}

The second trial was a much larger, double-blind randomised comparison with paroxetine.⁴⁰ This trial showed a significantly higher rate of response with mirtazapine at day 14 of the trial, and a faster rate of change in mean Hamilton Rating Scale for Depression scores overall. The authors also found that mirtazapine was significantly better tolerated than paroxetine, which is perhaps not surprising given the relatively poor adverse effect profile of paroxetine. The faster time to response with mirtazapine may be explained by the beneficial adverse effects of sedation resulting in improved sleep, as it has been generally well established that all antidepressants are roughly equal in terms of efficacy.

RECOMMENDATIONS

While there are a paucity of published data on the use of the new antidepressants in older patients, they are, nevertheless, widely used. Due to the limited number of published trials and their highly heterogeneous nature, specific treatment recommendations for depression in older patients are not supported by solid empirical evidence. It is well established that antidepressant efficacy in adults, as measured by response and remission rates, is equal among all classes of antidepressants. From this review, there is insufficient evidence to make such a generalisation to the elderly population as a group.

Most published data pertain to venlafaxine, which was shown to be equally efficacious with nortriptyline, sertraline and citalopram in the elderly population. Venlafaxine showed similar tolerability to either nortriptyline or fluoxetine, but sertraline and citalopram were better tolerated than venlafaxine.

Duloxetine demonstrated statistically significantly superior efficacy for response and remission when compared with placebo. In open-label trials duloxetine also showed response and remission, although at rates reflective of the different methods used for assessment. Rates of duloxetine withdrawal due to adverse events varied from 6 to 27%.

Although escitalopram showed varying rates of response in the elderly, clinical experience has shown it to be an effective and well-tolerated antidepressant with the added benefit of a relative lack of drug interactions.

Mirtazapine was efficacious and well tolerated in a specific nursing home population and better tolerated than paroxetine in older patients. Additionally, mirtazapine is available as a dispersible formulation, which is useful in patients with swallowing difficulties.

Clearly, further studies for the management of depression in older patients are needed in order to develop reliable and practical guidelines. Studies of the 'old old' as well as those that include comorbid medical illnesses and cognitive impairment are also needed.

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