Curr Geri Rep (2015) 4:301–311
DOI 10.1007/s13670-015-0140-y

The Pharmacology and Clinical Use of the Antidepressants Vilazodone, Levomilnacipran, and Vortioxetine for Depression in the Elderly

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Published online: 25 July 2015

Abstract Treatment of depression in the elderly is particularly challenging due to the relative scarcity of well-designed trials, atypical clinical presentations, and presence of multiple comorbidities, particularly cognitive impairment. While meta-analyses involving antidepressants have generally shown modest treatment benefits in this population, clinicians treating geriatric patients must be especially mindful of issues regarding polypharmacy, drug metabolism, and adverse event profiles. This article will examine the potential role in the elderly of the three latest antidepressants approved by the US Food and Drug Administration: vilazodone (January 2011), levomilnacipran (July 2013), and vortioxetine (September 2013). Thus far, vortioxetine was shown to be efficacious and tolerable in the elderly. Sub-group analyses involving vilazodone and levomilnacipran appear to show a similar efficacy in older compared with younger adults, although these are limited by small sample sizes. Issues related to pharmacodynamics, safety, tolerability, and the unique features associated with these drugs are further discussed.

Keywords Antidepressants · Depression · Elderly · Geriatric · Late-life · Levomilnacipran · Major depressive disorder · Vilazodone · Vortioxetine

This article is part of the Topical Collection on *Geriatric Psychiatry*

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Introduction

As one of the leading causes of disease burden, major depressive disorder (MDD) is a common and important public health priority [1]. The global burden of depressive disorders as measured by years lived with disability has increased by 37.5 % between 1990 and 2010 due almost entirely to population growth and aging [2]. Depression represents the most prevalent mental health problem among the elderly, with an estimated worldwide prevalence between 0.9 and 9.4 % in private households and 14 to 42 % in institutions depending on the study population involved [3]. Other studies involving the nursing home have shown a depression rate of 48 % and a prevalence three to four times higher than in community-dwelling elderly [4, 5]. While the incidence of depression in individuals greater than 70 years may not be higher than the incidence in younger individuals, the high prevalence among the elderly overall may indicate increased chronicity [6, 7]. Potential reasons for the high rates of chronic depression include increased rate of relapse and the presence of comorbidities [8].

Geriatric patients with depression often present as a challenge to clinicians due to atypical presentations, the presence of co-existing medical illness, and issues related to drug metabolism and adverse effects. Meta-analyses generally support the use of antidepressants in late-life depression [9–15]. As in younger adults, the treatment effect size is modest with one meta-analysis of ten trials involving elderly patients showing a pooled response rate of 44.4 % for drug versus 34.7 % for placebo [9]. Some problems with clinical trials involving the elderly include high placebo response rates, lack of generalizability due to the recruitment of patients without significant comorbidities, and high heterogeneity among studies [10, 16]. In another meta-analysis, antidepressant use was efficacious in patients aged 55 and older but not in a subset of six studies

involving patients with an age threshold of greater than 65 or 75 years [11]. Common first therapies in the elderly include the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), primarily due to their favorable adverse effect profiles and low cost [17•, 18]. A recent network meta-analysis showed clear evidence for the effectiveness of sertraline, paroxetine, and duloxetine in the elderly [19•]. The efficacy of the SSRIs and SNRIs is likely similar, with trials in the elderly comparing the SNRI venlafaxine with SSRIs finding no significant difference in efficacy [20]. While tricyclic antidepressants (TCAs) appear to have similar efficacy in the elderly compared with SSRIs, they are not as commonly used because some are highly anticholinergic, sedating, can cause or exacerbate orthostatic hypotension which can lead to falls, and have significant toxicity in overdose [10, 21]. Other agents such as trazodone, bupropion, and mirtazapine have also been studied in the elderly [22–24]. These drugs are sometimes used to take advantage of their side effect profiles, such as the use of trazodone in patients with depression and concomitant insomnia due to its sedating properties or the use of mirtazapine in depression with prominent appetite disturbance.

The most recent additions to the antidepressant landscape include vilazodone in January 2011, levomilnacipran in July 2013, and vortioxetine in September 2013 [25]. After a period of stagnation in antidepressant drug development in the first decade of the twenty-first century, the approval of these drugs offers clinicians with additional options [26]. The purpose of this review is to discuss the pharmacology, efficacy, safety, and tolerability of these new antidepressants in the context of current treatments for late-life depression.

Pharmacodynamics

Vilazodone

Vilazodone is classified as a serotonin partial agonist reuptake inhibitor (SPARI) because it inhibits the serotonin transporter (SERT) and is a partial agonist of the 5HT-1A receptor (Table 1) [27, 28]. Based on animal studies, vilazodone showed greater elevations of extracellular serotonin (5-HT) in the ventral hippocampus and frontal cortex and a 30-fold greater potency at inhibiting serotonin reuptake compared to the SSRI fluoxetine [29, 30]. Since 5-HT1A receptors function as pre-synaptic auto-receptors, 5-HT1A receptor partial agonists may decrease a negative feedback mechanism through rapid desensitization to achieve greater and faster increases in 5-HT [31, 32].

Levomilnacipran

Levomilnacipran inhibits both SERT and norepinephrine transporter (NET) (Table 1). Levomilnacipran is the more active enantiomer of milnacipran, currently available in Europe for treating depression and in the USA for treating fibromyalgia. The approved SNRIs duloxetine, venlafaxine, desvenlafaxine, and levomilnacipran differ in their preferential inhibition of SERT compared to NET. In vitro, levomilnacipran is unique among the approved SNRIs in that it displays an approximately 2-fold greater potency at inhibiting NE reuptake relative to 5-HT [33]. Venlafaxine appears to preferentially inhibit the SERT in vivo, while duloxetine may have a more balanced SERT and NET inhibition [34, 35]. Levomilnacipran may display a theoretical advantage in treating patients with symptoms associated with noradrenergic deficiencies, such as decreased concentration, loss of energy, and tiredness [36]. However, the clinical relevance of this unique receptor occupancy is not certain.

Vortioxetine

Vortioxetine is a multi-modal drug that acts as a SERT inhibitor, 5-HT1A receptor agonist, 5-HT1B receptor partial agonist, 5-HT1D, 5-HT3, and 5-HT7 receptor antagonist (Table 1). Vortioxetine has been shown to significantly increase levels of 5-HT, dopamine, and NE in areas important in depression, such as the ventral hippocampus and medial prefrontal cortex [37, 38]. Vortioxetine also modulates glutamatergic neurotransmission, possibly through its 5-HT3 antagonist properties [39, 40].

Pharmacokinetics

Vilazodone

In a single dose (20 mg) study involving 31 elderly subjects aged 65–80 years (mean age=68) and 12 younger subjects, elderly subjects showed a lower systemic exposure by ~20 % [41••]. This decrease was not considered clinically relevant, indicating that no dose adjustment is needed for elderly patients (Table 1). Vilazodone is highly protein bound (ranging from 96 to 99 %), extensively metabolized by the liver (particularly CYP3A4), and has a half-life of about 24 h [41••]. In vitro, vilazodone concentrations increased by ~50 % in the presence of the strong CYP3A4 inhibitor ketoconazole [42•]. No dose adjustment is needed based on age, gender, mild, moderate or severe renal impairment, or mild or moderate hepatic impairment.

Table 1 Pharmacokinetic and pharmacodynamic parameters for vilazodone, levomilnacipran, and vortioxetine

Drug	Mechanism of action	Half-life and protein binding	Metabolism	Dose adjustment based on age
Vilazodone [41••]	5-HT1A receptor partial agonist and SERT inhibitor	24 h; 96–99 % bound	Extensively metabolized by CYP3A4 (reduce dose to 20 mg if taking strong CYP3A4 inhibitor; increase dose with CYP3A4 inducer)	No dose adjustment (elderly subjects showed lower exposure by only ~20 %)
Levomilnacipran [43••]	SERT and NET inhibitor	12 h; 22 % bound	Excreted primarily by kidneys (do not exceed 80 mg/day in moderate renal impairment)	No dose adjustment (elderly subjects showed higher exposure by 24 %)
Vortioxetine [44••]	SERT inhibitor; 5-HT1A agonist; 5-HT1B partial agonist; 5-HT1D, 5-HT3, and 5-HT7 antagonist	66 h; 98 % bound	Extensively metabolized by CYP2D6 (reduce dose by half if taking strong CYP2D6 inhibitor; increase dose with CYP2D6 inducer)	No dose adjustment (pharmacokinetics similar in young and elderly subjects)

5-HT 5-hydroxytryptamine, *CYP* cytochrome P450, *NET* norepinephrine transporter, *SERT* serotonin transporter

Levomilnacipran

In one study, elderly subjects over the age of 65 had a higher exposure to levomilnacipran (Cmax by 24 % and area under the curve by 26 %) than younger subjects [43••]. However, no dose adjustment based on age is considered necessary (Table 1). Levomilnacipran is predominantly excreted by the kidney, and dosage adjustment is necessary for patients with moderate (creatinine clearance of 30–59 ml/min) or severe (creatinine clearance of 15–29 ml/min) renal impairment. No dose adjustment is necessary for mild, moderate, or severe hepatic impairment. The half-life is about 12 h, protein binding is about 22 %, and it is mostly excreted unchanged in the urine. The dose should not exceed 80 mg/day in the presence of a strong CYP3A4 inhibitor such as ketoconazole.

Vortioxetine

The pharmacokinetics of vortioxetine were similar in a single dose study involving elderly (>65 years old) compared with younger (24–45 years old) subjects [44••]. No adjustment is needed based on race, gender, age, mild to moderate hepatic impairment, or mild to end-stage renal impairment (Table 1). Vortioxetine has a half-life of 66 h, ~98 % plasma protein binding, and is extensively metabolized by several CYP enzymes through oxidation, especially CYP2D6.

Efficacy

Vilazodone

In a series of five 8-week phase II trials involving either fixed doses or flexible titration designs, treatment with vilazodone was not associated with statistically significant differences from placebo on the Hamilton Depression Rating Scale (HAM-D) [42•]. Three of the five trials also used active comparators (either fluoxetine or citalopram), which showed no significant differences from placebo. Several years later, two 8-week phase III trials that formed the basis for the FDA's approval showed that treatment with vilazodone resulted in significant improvements on the Montgomery-Åsberg Depression Rating Scale (MADRS) compared with placebo, with a least squares mean difference (LSMD) of −2.5 (p=0.009; d=0.23) and −3.2 (p=0.001; d=0.30) [45•]. The response rates (≥50 % decrease in MADRS score) in both studies were significant for vilazodone treatment versus placebo (40.4 vs. 28.1 %; 43.7 vs. 30.3 %, respectively). Remission rates (MADRS score <10) were numerically greater for vilazodone but not statistically significant. Two recent studies have also shown statistically significant improvements in favor of vilazodone compared with placebo [46, 47]. While vilazodone was proposed to have a faster onset of action due to its 5-HT1A receptor partial agonism, the clinical data thus far is not definitive [42•].

Efficacy data specifically in geriatric patients involves a subgroup analysis from the original two phase III trials (Table 2) [45•]. This subgroup of subjects ≥55 years (n=139) showed a non-statistically significant LSMD of −2.3 on the MADRS total score (p=0.161) compared with placebo. The LSMD on the MADRS was −2.8 points (p<0.001) in the group younger than 55 years (n=724). It should be noted that these results are based on a small sample size in a subgroup of patients above 55 years that may not accurately represent a geriatric population (patients above 70 years were excluded from the trials).

Levomilnacipran

The FDA evaluated five phase II/III studies ranging in length from 8 to 10 weeks prior to the approval of levomilnacipran. Two fixed-dose studies and two flexible-dose studies showed

Table 2 Efficacy data for vilazodone, levomilnacipran, and vortioxetine involving elderly patients

Drug	Population	Primary efficacy measure (compared with placebo)	Other comments
Vilazodone [45•]	Subgroup of subjects ≥55 (n=139) from two phase III trials	Non-significant LSMD of −2.3 points on MADRS (p=0.161)	
Levomilnacipran [48•]	Subgroup of subjects ≥60 (n=266) from five phase II and III trials	Significant LSMD of −4.4 points on MADRS (p=0.002)	Significant difference in response rate (17.9 %, p<0.01)
Vortioxetine [54••]	8-week Phase III trial in the elderly (n=452) with mean age of 71 years	Significant LSMD of −3.3 points on HDRS-24	Significant improvement on DSST and RAVLT compared with placebo

DSST Digit Symbol Substitution Test, *HDRS* Hamilton Depression Rating Scale, *LSMD* least squares mean difference, *MADRS* Montgomery-Åsberg Depression Rating Scale, *RAVLT* Rey Auditory Verbal Learning Test

significant differences from placebo on the MADRS. In these four studies, the LSMD from placebo ranged from −3.1 to −4.9 points on the MADRS [43••]. One flexible-dose study showed a numerical but not statistically significant advantage on the MADRS compared with placebo. None of these trials included an active comparator. In a pooled analysis of the five trials, the LSMD on the MADRS was −3.0 [48•].

A subgroup of subjects aged ≥60 years included 106 patients receiving placebo and 160 patients receiving levomilnacipran (Table 2) [48•]. Significant differences on the MADRS (−4.4 points, p=0.002) and response rate [17.9 %, p<0.01, number needed to treat (NNT)=6] were seen for levomilnacipran treatment compared with placebo. Both of these differences were the highest for any subgroup examined. No significant difference was seen in remission rates (8.6 %, NNT=12), although the difference in remission was similar to patients aged between 45 and 60 (9.7 %, p<0.001, NNT=11). While the mean age of this subgroup was not reported, this analysis may not represent a true geriatric population since the trials did not include any patients over the age of 80.

The Sheehan Disability Scale (SDS) was used throughout the clinical trials as a means to assess improvements in functional impairment across work/school, social, and family life settings. In a pooled analysis examining changes in SDS total score among the five trials, a subgroup of patients ≥60 years involved 85 patients receiving placebo and 125 patients receiving levomilnacipran [49]. Treatment with levomilnacipran was associated with a significant LSMD of −2.8 points on the SDS total score compared with placebo. This was similar to the LSMD in SDS total score of the overall pooled population (−2.2 points). The difference in response rates on the SDS was also significant (50.4 vs. 32.9 %; p=0.0327), while the difference in remission rate was not significant (24.8 vs. 18.8 %; p=0.5278).

Vortioxetine

The FDA evaluated ten short-term trials involving vortioxetine, of which six were considered positive [50•]. One of these studies was exclusively performed with elderly patients. Among the six positive trials, the difference in MADRS from placebo ranged from −2.8 to −7.1 [44••]. In one meta-analysis of the nine adult trials, the mean difference in MADRS total score for vortioxetine treatment compared with placebo was −2.6 (5 mg, p=0.008), −3.5 (10 mg, p<0.001), −2.6 (15 mg, p=0.105), and −4.5 points (20 mg, p<0.001) [51]. Response rates were statistically significant for the 5, 10, and 20 mg doses, and remission rates were statistically significant for the 10 and 20 mg doses. In another meta-analysis of 11 randomized controlled trials (RCTs), significant differences in MADRS total score from placebo were seen across all doses, ranging from −2.67 for the 5-mg dose to −5.20 for the 20-mg dose [52]. This study also found a lower response rate with vortioxetine treatment compared to the active SNRI comparators, although the trials were not designed to compare vortioxetine with active comparators. In a long-term maintenance study, patients receiving vortioxetine showed a statistically significant longer time to depression relapse compared with placebo [53].

The elderly study was an 8-week RCT involving 452 patients from 81 psychiatric, psychogeriatric, and geriatric settings in seven countries (Canada, Finland, France, Germany, Sweden, Ukraine, and USA) (Table 2) [54••]. Patients were randomized to either 5 mg/day vortioxetine, 60 mg/day duloxetine, or placebo. The mean age was 71 years, with the oldest patient being 88 years old. Ninety-five percent of the patients were Caucasian, and approximately two thirds were women. Inclusion criteria included at least one previous major depressive episode before the age of 60 years and without comorbid cognitive impairment (MMSE <24). The mean MADRS total score at baseline was around 30, indicating moderate-to-severe depression. A mean baseline Hamilton Rating Scale for Anxiety (HAM-A) total score of 19 indicated a high level of anxiety symptoms. A statistically significant difference from placebo on the Hamilton Depression Rating Scale (HDRS-24) was seen with vortioxetine (−3.3 points) and duloxetine (−5.5 points). Both vortioxetine and duloxetine also showed significant separation from placebo on response and remission rates. In the subset of patients from the USA (n=171), the difference in HDRS-24 total score from

placebo for treatment with vortioxetine or duloxetine was not significant, with an LSMD of −0.7 and −2.8, respectively [44••]. In non-US patients (n=277), the LSMD from placebo was −4.9 with vortioxetine and −7.1 with duloxetine.

Effects on Cognition

In older adults, depression is associated with an increased risk of cognitive impairment [55, 56]. However, the direction of causality is unclear since depressive symptoms may be early signs of dementia. Pre-clinical evidence suggested that vortioxetine may have cognitive enhancing properties via modulating multiple neurotransmitter systems, such as monoaminergic, cholinergic, and glutamatergic [57]. In rats, vortioxetine has been shown to enhance memory in novel object recognition and fear conditioning tasks [58]. Vortioxetine but not duloxetine or escitalopram reversed recognition and spatial deficits caused by 5-HT depletion [59, 60]. In the elderly study involving 5 mg/day vortioxetine, cognition was assessed as a predefined exploratory analysis by administering the Digit Symbol Substitution Test (DSST) (number of correct symbols) and Rey Auditory Verbal Learning Test (RAVLT) (acquisition and delayed recall) [54••]. While duloxetine only showed a statistically significant improvement on the RAVLT, vortioxetine treatment showed significant improvements on both the DSST and RAVLT compared with placebo. Path analysis showed that more than two thirds of the effect of vortioxetine on the DSST and RAVLT was a direct treatment effect rather than through improvements in depressive symptoms.

One 8-week study involving 10 and 20 mg/day vortioxetine assessed cognitive functioning as a primary efficacy measure in 602 depressed patients aged 18–65 years [61•]. The primary measure was a composite z-score comprising DSST and RAVLT scores. At endpoint, both doses of vortioxetine showed statistically significant improvements compared with placebo. The effect sizes on the DSST were 0.51 for 10 mg and 0.52 for 20 mg vortioxetine. Another 8-week study in depressed patients aged 18–65 years with self-reported subjective cognitive dysfunction showed significant improvements in cognitive functioning with vortioxetine compared with placebo [62]. Compared with placebo, the effect size on the primary efficacy measure, change from baseline to week 8 in DSST score, was 0.254 (p=0.019) for vortioxetine and 0.176 (p=0.099) for the active comparator duloxetine. In the path analysis, 75.7 % of the effect of vortioxetine on cognitive functioning was attributed to treatment independent of improvements in depressive symptoms.

In one phase III trial of levomilnacipran, 429 patients underwent cognitive assessments using the Cognitive Drug Research System (CDRS), which assesses power of attention (POA) and continuity of attention (COA) [63]. In a subgroup of 127 patients with combined POA and COA impairment, statistically significant improvements on the POA and COA were seen with levomilnacipran treatment compared with placebo.

Effects on Anxiety and Fatigue

The presence of anxiety in patients with late-life depression is common, with one study showing that 47.5 % of patients with MDD also met criteria for anxiety disorders [64]. Older patients with depression and generalized anxiety disorder (GAD) tend to have worse outcomes both in terms of functioning and response to treatment [65, 66].

Due to the potential role of the 5-HT1A receptor in generalized anxiety disorder (GAD), vilazodone may play an important role in treatment patients with MDD who also exhibit symptoms of anxiety [67]. In patients with GAD, treatment with vilazodone has shown positive improvements in phase III trials [68–70]. In two phase III trials involving patients with MDD and co-existing anxiety, post hoc analysis showed that treatment with vilazodone resulted in significant improvements on the HAM-A total and HAM-D17 Anxiety/Somatization subscale scores [71]. More recent trials in patients with MDD have demonstrated mixed results, with one study finding no significant difference for vilazodone on HAM-A scores compared with placebo [46, 47].

Levomilnacipran has not been evaluated as extensively in patients with concurrent anxiety. One post hoc analysis of five clinical trials examined the effect of levomilnacipran on improvement related to noradrenergic and anxiety symptom clusters [72]. The noradrenergic symptom cluster included scores related to concentration, lassitude, and anhedonia. The anxiety cluster included scores related to inner tension, agitation, and psychic and somatic anxiety. Treatment with levomilnacipran showed significant improvements in both symptom clusters compared with placebo, which also correlated with improvements in functional impairment based on the SDS. While there was some preliminary evidence showing significantly greater improvements on fatigue-related MADRS and HAM-D items, a RCT in patients with MDD and high levels of fatigue failed to detect significant improvements on fatigue outcomes with either levomilnacipran or SSRI treatment compared with placebo [73, 74].

Vortioxetine has been studied in patients with GAD with inconsistent results [75, 76]. With regard to adult patients with MDD, a meta-analysis of nine trials showed that treatment with vortioxetine in patients with high baseline anxiety (HAM-A score ≥20) was associated with significant improvements in MADRS total score and HAM-A total score compared with placebo [77]. These improvements on the HAM-A were also seen in the total MDD population. The study involving vortioxetine in elderly patients with MDD also reported

high levels of baseline anxiety, with a mean baseline HAM-A score of 19 [54••]. Treatment with vortioxetine in this study showed significant improvements in HAM-A total score from baseline to week 8 compared with placebo (LSMD=−2.35, $p<0.01$). This effect was numerically smaller when compared with duloxetine (LSMD from placebo of −3.54, $p<0.001$), although the study was not designed to compare the two drugs.

Safety and Tolerability

Minimizing treatment emergent adverse events (TEAEs) is an important component in the treatment of elderly patients. Elderly patients often present with several comorbidities and are more vulnerable to side effects due to physiologic changes associated with age. Side effects such as nausea, vomiting, or dizziness can dramatically increase morbidity. Sexual functioning also remains an important issue in late life [78]. Several current first-line antidepressants cause high rates of sexual dysfunction, with one study showing rates of 36–43 % for the SSRIs, mirtazapine, and venlafaxine [79, 80]. Thus, one potential reason to switch to a newer antidepressant would be related to tolerability.

Vilazodone

In general, the safety and tolerability profile for vilazodone is similar to the SSRIs. Adverse events (AEs) that occurred with vilazodone treatment that were ≥5 % and twice the frequency of placebo were diarrhea (28 %), nausea (23 %), sexual dysfunction (9 %), insomnia (6 %), and vomiting (5 %) [41••]. Discontinuations due to AEs were 7 % for vilazodone compared with 3 % for placebo. Patients in the ≥55 years subgroup treated with vilazodone experienced a similar incidence of TEAEs compared to the <55 years subgroup, with diarrhea occurring at a higher rate in the older age group [41••]. Mean changes in weight and vital signs were similar between vilazodone and placebo. No significant QTc prolongation was seen in a QT study [41••]. In the trials, no overdoses with vilazodone were lethal and exposure to vilazodone was low. While there was no evidence of hyponatremia in any of the phase II/III trials for vilazodone, the package insert still mentions the known risk of hyponatremia characteristic of certain antidepressants and especially seen in elderly patients [81].

Treatment with vilazodone was hypothesized to result in decreased incidence of sexual dysfunction due to its mechanism of action and the smaller extent of SERT inhibition than SSRIs [28]. In the phase III trials, sexual dysfunction was measured by the Arizona Sexual Experiences Scale (ASEX) and the Changes in Sexual Functioning Questionnaire (CSFQ) [82]. While the incidence of sexual dysfunction may appear lower than other SSRIs, the FDA felt that no definitive conclusion could be reached with regard to improvements in sexual dysfunction due to the lack of active comparator [42•]. In a study comparing vilazodone (20 and 40 mg/day), placebo, and the SSRI citalopram (40 mg/day), the incidence of AEs related to sexual functioning was greater for both vilazodone and citalopram compared with placebo [83]. On the CSFQ, all treatment groups experienced score improvements from baseline with no significant differences between treatment groups.

Levomilnacipran

Overall, the safety profile of levomilnacipran is similar to other SNRIs. In the subgroup of patients ≥55 years of age, 78.7 % of patients treated with levomilnacipran ($n=324$) experienced a TEAE compared with 55.5 % of patients treated with placebo ($n=218$) [43••]. AEs that occurred at ≥5 % and twice the frequency of placebo in this elderly subgroup included nausea (16.7 %), constipation (12.7 %), hyperhidrosis (10.8 %), dizziness (7.4 %), erectile dysfunction (5.6 %), and tachycardia (5.6 %). Incidence of hyperhidrosis was higher in the ≥55 years old group compared with the younger subgroup, while tachycardia, heart rate increase, vomiting, constipation, dizziness, and erectile dysfunction were not different between the two age groups. In the overall population, urinary hesitation and erectile dysfunction were seen with increased frequency at higher doses [43••]. Female patients experienced nausea (20.9 %) at almost twice the rate of male patients (10.6 %). The most common TEAEs leading to discontinuation were gastrointestinal in nature, including nausea and vomiting. Similar to other SNRIs, treatment with levomilnacipran among all patients in the short-term studies was associated with a mean increase in systolic blood pressure (SBP) of 3.0 mmHg, diastolic blood pressure (DBP) of 3.2 mmHg, and heart rate of 7.4 beats per minute (bpm) compared to a mean decrease of 0.4 mmHg in SBP, no change in DBP, and HR decrease of 0.3 bpm with placebo [84]. While the package insert mentions that the QTc was not prolonged to a clinically relevant extent, the FDA's medical review states that a significant but modest QTc prolongation was detected at therapeutic (120 mg) and supratherapeutic (300 mg) doses [43••]. No evidence of hyponatremia or significant effect on body weight was seen in the trials [85].

Overall, sexual dysfunction was more common with levomilnacipran treatment compared with placebo. The most common sexually related AEs included erectile dysfunction (5.9 %), ejaculation disorder (4.7 %), and testicular pain (3.8 %) [43••]. While the ASEX was used in one study showing improvement in both placebo and levomilnacipran groups, no active comparator was used [86].

Vortioxetine

Overall, vortioxetine displays a side effect profile similar to the SSRIs. Among short-term trials, common AEs for treatment with vortioxetine included nausea, vomiting, and constipation. In the MDD/GAD short-term trial pool, common TEAEs included nausea (23.9 %), vomiting (3.9 %), and constipation (4.4 %) [44••]. Nausea had a dose-related incidence, was seen in 15–20 % of patients in the first 1–2 days, and was the most common TEAE leading to discontinuation. No significant weight gain or changes in vital signs, ECG, and laboratory parameters were seen. Two cases of hyponatremia were identified during trials involving vortioxetine, which were considered possibly related to treatment [44••].

In the 8-week elderly study, 62 % of patients receiving vortioxetine 5 mg experienced one or more AEs compared with 61 % of patients receiving placebo and 78 % of patients receiving duloxetine [54••]. Nausea was the only AE with a significantly higher incidence in vortioxetine-treated patients (21.8 %) compared with placebo (8.3 %). Six male patients in the duloxetine group experienced AEs related to sexual dysfunction compared with no patients receiving placebo or vortioxetine. The percentage of patients who discontinued due to AEs was 3 % for placebo, 6 % for vortioxetine, and 10 % for duloxetine.

The ASEX was used to assess sexual functioning in six short-term MDD trials and one GAD trial involving vortioxetine. A pooled analysis showed no significant difference in risk of developing treatment emergent sexual dysfunction (TESD) for patients without sexual dysfunction at baseline with vortioxetine or placebo treatment [87]. For patients aged >50 years, the incidence of TESD with vortioxetine treatment (n=153) was not statistically significantly higher than placebo (n=65) for any dose. TESD with duloxetine treatment (n=47) was significantly higher when compared with vortioxetine 5 mg (n=25) and 10 mg (n=55). These results are limited given the small samples sizes. In one study designed to compare vortioxetine to escitalopram on sexual functioning in patients currently treated with an SSRI and experiencing TESD, patients switched to vortioxetine compared with escitalopram showed significant improvements in CSFQ-14 total score after 8 weeks (mean difference of 2.2 points; p=0.013) [88]. A non-significant increase was seen in the number of patients treated with vortioxetine who shifted to normal sexual functioning (OR=1.37; p=0.112).

Discussion

Due to cost and limited data regarding efficacy and tolerability in the elderly, the three newest antidepressants are not currently recommended as first line for treatment of MDD in elderly patients. Based on the studies discussed previously, it does seem warranted to consider these new drugs as an alternative once a first-line antidepressant shows inadequate response or is not tolerable.

Efficacy data for these drugs is limited to one positive elderly study involving vortioxetine. The elderly subgroup analyses for vilazodone and levomilnacipran showed improvements on primary efficacy measures compared with placebo that were similar to younger subgroups. However, the relatively small sample size and post hoc nature of these analyses limits any definitive conclusion regarding the efficacy in the elderly. Further efficacy and safety data for vilazodone will be provided by a phase IV pilot study currently recruiting participants to compare vilazodone to paroxetine in patients ≥60 years [89]. Clinicians may be hesitant to switch to levomilnacipran after treatment failure with a different SNRI. Levomilnacipran may have a unique effect on the noradrenergic symptom cluster (e.g., decreased concentration, loss of energy) compared with other SNRIs due to its 2-fold greater affinity for the noradrenergic receptor in vitro. While there is some preliminary clinical evidence showing improvement in noradrenergic symptom cluster scores, the clinical relevance cannot yet be determined and levomilnacipran was not shown to improve fatigue outcomes in patients with MDD and high levels of fatigue [72, 74]. Levomilnacipran may theoretically be an option in patients with MDD and concomitant fibromyalgia, although only milnacipran is currently approved for the management of fibromyalgia. The elderly study involving vortioxetine provides positive data demonstrating the efficacy of 5 mg/day vortioxetine compared to placebo in a population with an average age of ~71 years [54••]. Interestingly, the LSMD on the HDRS-24 was non-significant in the US subgroup for treatment with vortioxetine and duloxetine compared with placebo [44••]. Since this diminished effect was seen in both vortioxetine and duloxetine treated groups, it may be related to signal detection or an unknown variable rather than vortioxetine's efficacy. Vortioxetine was well tolerated in this study compared with placebo, which could be related to the low dose (5 mg/day) used in the study. While the package insert recommends a starting dose of 10 mg/day, it seems reasonable in elderly patients to begin at 5 mg/day to assess tolerability and efficacy before attempting to increase the dose. The cognitive enhancing properties of vortioxetine in this elderly study are also worth mentioning. Since patients in this study were required to have an MMSE of at least 24, no definitive conclusion can be drawn regarding its potential effect in patients with dementia. However, a therapeutic trial may be warranted for patients presenting with depression and deficits in cognition.

The utility of these drugs in patients with MDD and high levels of anxiety remains unclear. While it appears that vilazodone has the greatest evidence of the three to support its use in this setting, these studies were all performed in adults and may not fully translate to elderly patients. It does appear

that vortioxetine could play a role in this setting given that the elderly study was efficacious on MADRS and HAM-A scores in patients with MDD who incidentally had high levels of baseline anxiety.

Another important issue related to choosing among alternative antidepressants involves the safety and tolerability profile. All three new drugs do not require dosage adjustments based on age and in most patients with renal or hepatic impairment. While it appeared that vilazodone may have a limited effect on sexual dysfunction, the results from a trial with escitalopram as the active comparator did not show a significant difference. It seems likely that vilazodone is no worse than the SSRIs, but it has not been conclusively shown to be better. Levomilnacipran appears to show a profile similar to other SNRIs, with increases in blood pressure and urinary hesitancy being two important AEs. It is recommended for patients to have their blood pressure stabilized prior to treatment and regularly monitored. This may make levomilnacipran a less desirable option given the high prevalence of hypertension in the elderly [90]. The major tolerability concern with vortioxetine is nausea, which was generally seen early after initiation in the clinical trials. Given the dose relationship seen with nausea, starting with the lowest dose (5 mg/day) would presumably allow for decreased incidence of AEs and was still effective in the elderly trial. Vortioxetine may have the most promising data of the three with regard to sexual functioning, showing significant improvements on the CSFQ compared with escitalopram in patients who responded to an SSRI and experienced treatment-emergent sexual dysfunction [88]. However, the FDA's recommended efficacious dose for vortioxetine is 20 mg/day, which showed rates of sexual dysfunction in the clinical trials that were similar to the active comparator duloxetine.

Conclusion

Physicians looking to switch elderly patients to any of the three newest antidepressants will find a lack of evidence supporting their use. Based on the limited data thus far, it seems reasonable that vilazodone, levomilnacipran, or vortioxetine would be efficacious and tolerable in elderly patients. More trials in geriatric populations will be needed especially given the high prevalence of depression in the elderly and the aging of the population. Head-to-head trials comparing the new agents to the other SSRIs and SNRIs, trials enrolling patients over the age of 85, and more "real world" trials that involve patients with multiple comorbidities will allow for more informed clinical decision making.

Compliance with Ethics Guidelines

Conflict of Interest William James Deardorff declares that he has no conflict of interest.

George T. Grossberg has received grants for his department from Actavis, Novartis, Accera, and Noven, and has received personal fees from Actavis, Takeda, Otsuka, Novartis, Genentech, and Roche.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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