Venlafaxine and duloxetine: A comparison of efficacy and tolerability for the treatment of depression in elderly patients

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ABSRACT

The geriatric population has a disproportionally higher rate of depression and related suicide compared to the general population. While selective serotonin reuptake inhibitors are considered first line, serotonin norepinephrine reuptake inhibitors (SNRIs) are commonly used. Online databases including MEDLINE, EMBASE, International Pharmaceutical Abstracts, and CINAHL were searched (up to June 2013) to identify trials using SNRIs in the elderly. Results revealed 15 studies involving venlafaxine (n=10) and duloxetine (n=5) use in the elderly. Overall, venlafaxine and duloxetine appear to be similar in efficacy and tolerability in treating late life depression. However, venlafaxine has been more extensively studied in this particular population, appears to carry fewer drug interactions, and is available in generic forms for regular and extended-release formulations. Doses greater than 225 mg/day for venlafaxine or 60 mg/day for duloxetine appear to lead to greater discontinuation rates.

KEYWORDS

Venlafaxine, duloxetine, depression, elderly, geriatric

INTRODUCTION

According to the National Institute of Mental Health, the geriatric population has a disproportionally higher rate of depression and related suicide. Elderly individuals often experience undiagnosed depressive symptoms or depression secondary to other medical conditions (e.g. Alzheimer's disease, Parkinson's disease, cancer).[1] Complicating matters among the elderly include the fear of increased rates of adverse reactions and drug interactions, especially due to the increasing incidence of polypharmacy and comorbidities. Common adverse effects of antidepressants, such as anticholinergic effects, can complicate these medical conditions. Therefore, investigation into the efficacy and tolerability of antidepressants among the elderly is of compelling interest.

The most commonly prescribed class of antidepressants in the elderly is the selective serotonin reuptake inhibitors (SSRIs) and these are some of the first-line agents available.[2] Serotonin norepinephrine reuptake inhibitors (SNRIs) are a newer and smaller class of antidepressants often referred to as "dual-action" antidepressants which include agents such as nefazodone, venlafaxine, duloxetine, desvenlafaxine, and levomilnacipran. They are usually prescribed in the elderly when treatment is not successful with an SSRI. Currently, nefazodone has been withdrawn from the U.S. market and is seldom used due to hepatic toxicity. Additionally, there are presently no published data available for newer agents such as desvenlafaxine or levomilnacipran specifically focused in the elderly population. As a result, venlafaxine and duloxetine are the SNRIs most commonly used in the elderly population. No recent studies have specifically focused on the efficacy and tolerability of venlafaxine compared directly to duloxetine in the treatment of depression in the elderly. Therefore, the purpose of this review is to examine the efficacy and tolerability of venlafaxine and duloxetine in the elderly.

METHODS

Online databases including MEDLINE, EMBASE, International Pharmaceutical Abstracts, and CINAHL were searched (up to June 2013). Search terms included elderly, geriatric, depression, antidepressants, venlafaxine, duloxetine, and levomilnacipran. Search limits included human only, English only, and peer-reviewed journals. References from all articles identified were examined for additional citations. Randomized, blinded trials and open label studies with an age range of 55 years and over were included in the analysis. Studies were selected based on relevance to the topic and inclusion of adverse effects, HAM-D and/or MADRS scores, remission rates, and discontinuation due to adverse effects. Studies in which elderly patients could not be separated out from the sample size were excluded. Case reports and case series were also excluded from this review. Conversions of MADRS to HAM-D 17 scores were calculated with the equation (HAM-D 17 = -1.58 + 0.86 x MADRS) provided by Heo et al whenever possible.[3]

RESULTS

A literature search revealed 15 studies involving venlafaxine (n=10) and duloxetine (n=5) use in the elderly. Six out of the 10 studies with venlafaxine included randomized controlled trials which lasted between 6 weeks and 6 months with sample sizes ranging from 31 to 300 subjects (See Table 1).[4-9] These studies showed a dosing range of 18.75 mg/day to 375 mg/day.[7,8] Venlafaxine was compared to citalopram, nortriptyline, sertraline, and fluoxetine.[4,6-9] The remaining studies (n=4) were open label with doses ranging from 75 mg/day to 225 mg/day, lengths of 24 weeks to 24 months and sample sizes between 28 and 1,214 subjects (See Table 2).[10-13]

There were two randomized controlled studies comparing duloxetine to placebo and 3 open label trials.[15-19] The placebo-controlled trials had duloxetine doses of 60 mg/day, lasted 8 and 9 weeks, and had samples sizes of 90 and 311 subjects (See Table 3).[15,16] The three open label duloxetine studies showed a dosing range of 30 mg/day to 120 mg/day (See Table 4).[17-19] Length of these studies ranged from 12 weeks to 52 weeks and sample sizes of 30 to 101 subjects.[18,19]

Efficacy

Venlafaxine was shown to have similar efficacy rates compared to other antidepressants in randomized controlled trials. In one particular study, higher rates of remission were reported for venlafaxine (37.5 to 225 mg/day) compared to placebo and fluoxetine (20 to 60 mg/day); however, results were not statistically significant (p=0.549).[9] In randomized controlled trials, venlafaxine improved HAM-D 17 scores by 4.6 points in one study, improved MADRS scores between 13-18 points, and achieved remission in approximately 19-71% of patients.[4,5,7,8] In open-label trials, venlafaxine improved HAM-D 17 scores by 16.4 points in one study and achieved remission in approximately 57-70% of patients.[10-13]

Currently, duloxetine has not been studied against other antidepressants for the treatment of depression in elderly patients. Two randomized controlled trials demonstrated duloxetine (60 mg/day) was more effective than placebo (p=0.014, p<0.001).[15,16] Duloxetine, in randomized controlled trials, improved HAM-D 17 scores between 6.5-10.8 points and achieved remission in approximately 27-44% of patients. Open label studies with duloxetine showed improvement in HAM-D 17 scores by 17.5 points and MADRS scores by 11.7 points.[18,19] Remission was achieved in approximately 41-72% of patients.

Safety

In the randomized controlled trials, the most common side effects reported with venlafaxine were nausea and headache (See Table 5). Venlafaxine displayed a large range of discontinuation rates (2.9% - 27%) due to adverse effects. Furthermore, venlafaxine had higher discontinuation rates in trials than placebo, citalopram, sertraline, and fluoxetine, but the same or lower rates compared to nortriptyline. Dry mouth, dizziness and nausea appeared to be the most commonly reported adverse effects with duloxetine. Duloxetine also showed wide discontinuation rates (9.7% - 27%) due to adverse effects such as dizziness, nausea, and constipation (See Table 5). Duloxetine had a higher discontinuation rate than placebo in one trial and a similar rate in another.

DISCUSSION

Data directly comparing venlafaxine and duloxetine in the geriatric population are lacking. Also, most controlled studies using venlafaxine use the MADRS while all duloxetine controlled studies use HAM-D 17, making comparisons difficult. When calculated and compared using the equation provided by Heo et al, overall venlafaxine and duloxetine show similar improvement in HAM-D scores. Controlled trials with venlafaxine and duloxetine appear to improve HAM-D 17 scores similarly.[4,5,7,8,15,16] Studies lasting more than 24 weeks with venlafaxine improved HAM-D 17 scores by over 15 points and achieved remission in approximately 20-70% of patients.[4,6,11-13] Generally, the longer the duration of the trial, the greater the improvements in the MADRS and

HAM-D were observed. Trials lasting less than 24 weeks[5,7-9] improved HAM-D 17 scores between 5-13 points and achieved remission in at least 27% of patients. The one study lasting more than 24 weeks with duloxetine improved HAM-D scores by 17.5 points and achieved remission in 72% of patients.[19] Other trials with duloxetine which lasted less than 24 weeks improved HAM-D scores between 7-12 points and achieved remission in at least 27% of patients.[15,16,18] This suggests elderly individuals may take longer to respond to both of these agents and that continued improvement is seen over time.

Safety and tolerability appear to be similar between the two medications. Anticholinergic side effects are of particular concern in the geriatric population as they place these patients at risk for falls and other undesirable side effects. Neither venlafaxine nor duloxetine has been found to have significant binding affinity for cholinergic receptors (K_i > 1mM) despite a noticeable incidence of classic anticholinergic adverse events for both agents.[20] Despite the data on receptors, anticholinergic side effects including dry mouth and constipation were regularly reported in trials with venlafaxine and duloxetine. Dizziness was commonly reported in approximately 20% of subjects taking venlafaxine and duloxetine. Headache and sweating appear to be more common with venlafaxine and agitation with duloxetine. Studies with duloxetine doses of 80 mg/day or above resulted in more discontinuations due to adverse events than those using the recommended dose of 60 mg/day. Although receptor data state anticholinergic effects are minimal, clinical data on the geriatric population suggest otherwise. Therefore, geriatric patients should be monitored closely for anticholinergic side effects (e.g., constipation, dry mouth, dizziness).

Unlike venlafaxine, duloxetine is highly protein bound in human plasma and, therefore, may be more likely to interact with medications such as warfarin.[21] Smokers can potentially have lower levels of duloxetine due to its metabolism by CYP1A2. Although a dose increase of about 15-30% is necessary to compensate for the increased metabolism, it is recommended to start duloxetine at the normal dose and adjust according to clinical efficacy and tolerability.[22,23] Duloxetine is also a moderate inhibitor of Cytochrome P450 2D6 which may pose a risk with drug interactions. In one study, duloxetine (60 mg twice daily) increased the area under the curve (AUC) and peak concentration (C_{max}) of metoprolol by 180% and 100%, respectively.[24]

Initial doses of venlafaxine in controlled and open-label trials ranged from 18.75 – 75 mg/day. While maximum doses ranged from 131.25 – 375 mg/day, patients were usually only titrated to maximum doses under the discretion of the investigator. As a result, it is recommended when deciding on a titration schedule that consideration is given to the individual patient's response to medication especially when targeting higher doses. Overall, based on the published studies, venlafaxine should be initiated at 18.75 – 37.5 mg/day and the first dose may be increased after a minimum of one week. Gradual titration over the course of several weeks to a target dose of 150 – 225 mg/day is recommended as tolerated. Doses beyond 225 mg/day showed an increase in adverse effects.[10,11] While clinically significant response may take several weeks, optimal clinical efficacy may take closer to six months.

In randomized controlled trials of duloxetine, patients were initiated at 60 mg/day. All patients were maintained at this dose until the end of the study. In open-label trials of duloxetine, dosing and titration varied. Starting doses ranged from 30 – 80 mg/day and patients were titrated up to 120 mg/day based on the clinician's judgment. Maximum doses were 60 mg/day and 120 mg/day in randomized, controlled and open-label trials, respectively. Even though some studies used an initial starting dose of 60 mg, it appears that duloxetine may be best if initiated at 30 mg/day and increased after one week to 60 mg/day. After six weeks at 60 mg, patients can be titrated to a maximum of 120 mg/day, as tolerated.

CONCLUSION

Venlafaxine and duloxetine appear to be similar in efficacy and tolerability in treating late life depression. Doses greater than 225 mg/day for venlafaxine or 60 mg/day for duloxetine appear to lead to greater discontinuation rates. Overall, venlafaxine has been more extensively studied in this particular population, appears to carry fewer drug interactions, and is available in generic forms for regular and extended-release formulations. Based on these advantages, venlafaxine appears to be the preferred SNRI to treat depression in the elderly population.

Table 1. Venlafaxine – Controlled Trials

Study	Population / Setting	Study Design	Drug	Dose (mg/day)	Study Size (n)	Results	Adverse effects
Allard et al (2004)[4]	>65 MADRS > 20 MMSE > 24 Outpatients	6 months RCT, double-blind	Venlafaxine	37.5–150 (mean dose not available)	73	MADRS decreased from 27.6 to 9.6 after 22 weeks 19% remission rate (MADRS < 10)	dry mouth (12%), constipation (6.6%) 8.2% discontinued due to AE
			Citalopram	10–30 (mean dose not available)	75	MADRS decreased from 27.0 to 9.6 after 22 weeks 23% remission rate (MADRS < 10)	dry mouth (11%), dizziness (5.3%) 4% discontinued due to AE
de Vasconcelos Cunha et al (2007)[5]	>60 Dementia (MMSE 10-24) Outpatients	6 weeks RCT, double-blind	Venlafaxine	37.5–131.25 (mean 75)	14	MADRS decreased from 24.5 to 11.4	agitation (14%), tremor (14%), psychotic symptoms (15%) 14.3% discontinued due to AE
			Placebo		17	MADRS decreased from 24.5 to 12.2	elevated BP (12%), insomnia (12%) 0% discontinued due to AE
Gastó et al (2003)[6]	>65 In- and out-patients HAM-D 17 > 21	6 months RCT, single-blind	Venlafaxine	75-300 (mean 251.5)	34	71% remission rate (HAM-D 17 score < 7)	orthostatic vertigo (52.9%), sweating (41.2%) 2.9% discontinued due to AE
			Nortriptyline	50-100 (mean 62.5)	34	70% remission rate (HAM-D 17 score < 7)	dry mouth (67.6%), sweating (35.3%) 2.9% discontinued due to AE
Kok et al (2007)[7]	>60 MADRS > 20 MMSE > 15 Inpatients	12 weeks RCT, double-blind	Venlafaxine	75-375 (mean 156)	40	27.5% remission rate (MADRS < 10) MADRS decreased from 32.9 to 19.8	5.2 mean side effects per patient dry mouth (50%) 4% discontinued due to AE
			Nortriptyline	25-200 (mean 94.5)	41	36.6% remission rate (MADRS < 10) MADRS decreased from 32.9 to 16.6	5.6 mean side effects per patient dry mouth (88%) 12% discontinued due to AE
Oslin et al (2003)[8]	Mean age: 82.5 Nursing Home	10 weeks RCT, double-blind	Venlafaxine	18.75-150 (mean dose not available)	27	HAM-D reduced from 20.3 to 15.7	Specific AE frequency not available 15% discontinued due to AE
			Sertraline	25-100 (mean dose not available)	25	HAM-D reduced from 20.2 to 12.2	Specific AE frequency not available 4% discontinued due to AE
Schatzberg and Roose (2006)[9]	>65 HAM-D 21 > 20 MMSE > 18 Non-residential setting	8 weeks RCT, double-blind	Venlafaxine	37.5-225 (mean dose not available)	104	27% remission rate (HAM-D 21 score < 7)	nausea (45%), headache (26%) 27% discontinued due to AE
			Fluoxetine	20-60 (mean dose not available)	100	20% remission rate (HAM-D 21 score < 7)	nausea (23%), headache (18%) 19% discontinued due to AE
			Placebo		96	24% remission rate (HAM-D 21 score < 7)	headache (22%), dry mouth (15%) 9% discontinued due to AE

Adverse event (AE); Clinical Global Impression - Severity Scale (CGI-S); Hamilton Depression Rating Scale (HAM-D); Mini Mental State Exam (MMSE); Montgomery–Åsberg Depression Rating Scale (MADRS); Randomized Controlled Trial (RCT); Selective serotonin reuptake inhibitor (SSRI)

Table 2. Venlafaxine – Open-Label Trials

Study	Population / Setting	Study Design	Drug	Dose (mg/day)	Study Size (n)	Results	Adverse effects
Amore et al (1997)[10]	>65 Outpatients	24 months Open-label	Venlafaxine	75-225 (mean 112.5)	28	75% response rate (HAM-D 21 < 11)	nausea (20%), palpitations (8%), insomnia (20%), postural hypotension (8%) 4% discontinued due to AE
Baca et al (2006)[11]	>80 Outpatients	24 weeks Open-label	Venlafaxine	75-225 (mean 94.2)	95	57.1% remission rates (HAM-D 17 score < 7) HAM-D 17 reduced from 23.6 to 7.2	7.2% reported AE Specific AE frequency not available 5% discontinued due to AE
Cervera-Enguix et al (2004)[12]	>60 HAM-D 17 > 14 Outpatients	6 months Open-label, Observational	Venlafaxine	75-150 (mean 84.3)	1214	70.2% remission rates (HAM-D 17 score < 7) 83.2% response rate (HAM-D 17 decreased 50%)	4.6% reported AE dizziness (<1%), nausea (<1%) 1.4% discontinued due to AE
Ibor et al (2008)[13]	>65 Outpatients	24 weeks Open-label	Venlafaxine	75-225 (mean 109.3)	59	59.2% remission rate (HAM-D 17 score < 7) 81.6% response rate (HAM-D 17 decreased 50%)	6.8% reported AE xerostomia (3.4%) 1.7% discontinued due to AE

Adverse event (AE); Clinical Global Impression - Severity Scale (CGI-S); Hamilton Depression Rating Scale (HAM-D); Mini Mental State Exam (MMSE); Montgomery–Åsberg Depression Rating Scale (MADRS); Randomized Controlled Trial (RCT); Selective serotonin reuptake inhibitor (SSRI)

Table 3. Duloxetine – Controlled Trials

Study	Population / Setting	Study Design	Drug	Dose (mg/day)	Study Size (n)	Results	Adverse effects
Nelson et al (2005)[15]	>55 Pain symptoms HAM-D 17 > 15 CGI-S > 4 Setting not available	9 weeks RCT, double-blind	Duloxetine	60 (mean 60)	47	HAM-D 17 reduced from 20.7 to 9.9 44.1% remission rate (HAM-D 17 score < 7)	nausea (25.2%), dry mouth (22.7%), constipation (16.0%), decreased appetite (11.8%), insomnia (11.8%), fatigue (9.2%), decreased libido (7.6%) 21% discontinued due to AE
			Placebo		43	HAM-D 17 reduced from 20.0 to 12.86 16.1% remission rate (HAM-D 17 score < 7)	nausea (10.0%), dry mouth (6.7%), constipation (5.6%), decreased appetite (3.3%), insomnia (3.3%), fatigue (2.2%), decreased libido (0%) 6.7% discontinued due to AE
Raskin et al (2007)[16]	>65 HAM-D 17 > 18 MMSE > 20 Outpatients	8 weeks RCT, double-blind	Duloxetine	60 (mean 60)	207	27.4% remission rate (HAM-D 17 score < 7) HAM-D 17 reduced from 22.4 to 15.91	dry mouth (14.5%), nausea (12.6%), diarrhea (8.2%) 9.7% discontinued due to AE
			Placebo		104	14.7% remission rate (HAM-D 17 score < 7) HAM-D 17 reduced from 22.0 to 18.28	dry mouth (1.9%), nausea (3.8%), diarrhea (1.9%) 8.7% discontinued due to AE

Adverse event (AE); Clinical Global Impression - Severity Scale (CGI-S); Hamilton Depression Rating Scale (HAM-D); Mini Mental State Exam (MMSE); Montgomery–Åsberg Depression Rating Scale (MADRS); Randomized Controlled Trial (RCT); Selective serotonin reuptake inhibitor (SSRI)

Table 4. Duloxetine – Open-Label trials

Study	Population / Setting	Study Design	Drug	Dose (mg/day)	Study Size (n)	Results	Adverse effects
Karp et al (2008)[17]	>65 SSRI resistant depression HAM-D 17 > 15 MMSE > 18 Outpatients	16.5 weeks Open label	Duloxetine	30-120 (mean 93)	40	50% response rate (HAM-D 17 score < 10)	12.5% discontinued due to AE Specific AE frequency not available
Karp et al (2010)[18]	>60 Chronic back pain MADRS > 15 MMSE > 20 Outpatients	12 weeks Open label	Duloxetine	30-120 (median dose 90; mean dose not available)	30	46.7% remission (MADRS < 9) MADRS decreased from 22.0 to 10.3	Specific AE frequency and discontinuation rate not available
Wohlreich et al (2004)[19]	>65 Subset of larger study CGI-S > 3 Outpatients	52 weeks Open label	Duloxetine	80-120 (mean 99.7)	101	41.4% remission rate (HAM-D 17 score < 7) at 6 weeks HAM-D 17 reduced from 21.8 to 8.8 at 6 weeks 69.8% remission rate (HAM-D 17 score < 7) at 28 weeks HAM-D 17 reduced to 4.4 at 28 weeks 72.3% remission rate (HAM-D 17 score < 7) at 52 weeks HAM-D 17 reduced to 4.3 at 52 weeks	Nausea (28.7%), dizziness (26.7%) 27% discontinued due to AE

Adverse event (AE); Clinical Global Impression - Severity Scale (CGI-S); Hamilton Depression Rating Scale (HAM-D); Mini Mental State Exam (MMSE); Montgomery–Åsberg Depression Rating Scale (MADRS); Randomized Controlled Trial (RCT); Selective serotonin reuptake inhibitor (SSRI)

Table 5. Treatment-Emergent Adverse Events

Venlafaxine

Study	Dry Mouth	Agitation/ Insomnia	Nausea/ Vomiting	Dizziness	Consti-pation	Headache	Sweating	Tremor	Decreased Appetite	Fatigue	Diarrhea
Allard et al[4]	12	3.9		3.9	6.6					2.6	
de Vasconcelos Cunha[5]		14						14			
Gasto et al[6]	17.6	17.6	17.6	52.9	20.6	26.5	41	11.8			
Kok et al[7]	50										
Schatzberg and Roose[9]	23	10	45	17	22	26	11	6	11	12	12
Amore et al[10]	5	5	20	8							
Ibor et al[13]	3.4										
Khan et al[14]	31	31	36	28	26	43	31		19	26	

Duloxetine

Study	Dry Mouth	Agitation/ Insomnia	Nausea/ Vomiting	Dizziness	Consti-pation	Headache	Sweating	Tremor	Decreased Appetite	Fatigue	Diarrhea
Nelson et al[15]	22.7	11.8	25		16.00				11.8	9.2	
Raskin et al[16]	14.5		12.6	8.2	10.10					6.3	8.2
Wohlreich et al[19]	17.8	21.8	28.7	30.7	22.80	15.8	14.9	8.90	7.9	22.8	16.8

Adverse event (AE); Clinical Global Impression - Severity Scale (CGI-S); Hamilton Depression Rating Scale (HAM-D); Mini Mental State Exam (MMSE); Montgomery–Åsberg Depression Rating Scale (MADRS); Randomized Controlled Trial (RCT); Selective serotonin reuptake inhibitor (SSRI)

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