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REVIEW

Duloxetine in the treatment of generalized anxiety disorder

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Abstract: Duloxetine is a serotonin-norepinephrine reuptake inhibitor (SNRI) which is FDA approved for the treatment of generalized anxiety disorder (GAD) in doses of 30 mg to 120 mg daily. Duloxetine has been shown to significantly improve symptoms of GAD as measured through the Hamilton Anxiety Rating Scale (HAMA), the Clinical Global Impressions Scale (CGI-I), and other various outcome measures in several placebo-controlled, randomized, double blind, multi-center studies. Symptom improvement began within the first few weeks, and continued for the duration of the studies. In addition, duloxetine has also been shown to improve outcomes in elderly patients with GAD, and in GAD patients with clinically significant pain symptoms. Duloxetine was noninferior compared with venlafaxine XR. Duloxetine was found to have a good tolerability profile which was predictable and similar to another SNRI, venlafaxine. Adverse events (AEs) such as nausea, constipation, dry mouth, and insomnia were mild and transient, and occurred at relatively low rates. It was found to have a low frequency of drug interactions. In conclusion, duloxetine, a selective inhibitor for the serotonin and norepinephrine transporters, is efficacious in the treatment of GAD, and has a predictable tolerability profile, with AEs generally being mild to moderate.

Keywords: duloxetine, generalized anxiety disorder, anxiety, GAD

Introduction

Generalized anxiety disorder (GAD) is a serious and potentially debilitating psychiatric disorder characterized by generalized and persistent excessive anxiety, accompanied by other psychological or somatic symptoms (eg, palpitations, sweating, sleep disturbances).[1,2] Symptoms for GAD diagnosis, which must be present for at least 6 months (according to DSM–IV and ICD-10 criteria) can be found in Table 1.

GAD is a common disorder, with a lifetime and 12-month prevalence in the US of 4.1% and 2.1%, respectively.[3] In Europe, the lifetime prevalence was found to be similar at 4.3% to 5.9%.[2] GAD often coexists with other psychiatric disorders, such as major depressive disorder (MDD), panic disorder (PD), or alcohol and substance abuse.[1] The most common of these psychiatric comorbidities is MDD which is observed in almost two thirds of patients.[4] As well as psychiatric comorbidities, GAD is also comorbid with a number of medical conditions including cardiovascular disease, stroke, peptic ulcer disease, irritable bowel syndrome, pain, and headache.[1] The high prevalence of GAD and its comorbid conditions results in a substantial financial burden as well as a personal one. In fact, some estimates put the US economic cost of anxiety disorders, inclusive of GAD, at US$42 to US$63 billion per year.[5,6] A recent retrospective review of healthcare claims in patients

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Table 1 Symptoms of generalized anxiety disorder[1]

Psychological symptoms	Physical symptoms
Excessive anxiety	Fatigue
Inability to control worries	Restlessness
Difficulty concentrating	Muscle tension
Feeling "on edge"	Nausea and diarrhea
	Palpitations
	Sweating

with GAD found an average annual cost of US$7,451 per patient, and that 77% of these patients had either comorbid pain or depression.[7] The disease is almost twice as common in women than men, generally appears in childhood or late adolescence, and has a median duration of 15.6 years;[8] however it can appear later in life, and is often precipitated by a life-changing event.[8]

It is hypothesized that GAD is the result of neurobiological dysfunction of the serotonergic, noradrenergic, or GABAergic systems,[2] and medications that have an effect on these systems are able to reduce GAD symptoms.[9] The use of buspirone, selective serotonin (5-HT) reuptake inhibitor (SSRI) antidepressants and/or benzodiazepines are commonly prescribed as first-line agents in treating GAD, followed by serotonin/norepinephrine reuptake inhibitor (SNRI) antidepressants, mirtazapine, or a monoamine oxidase inhibitor (MAOI). If unsuccessful with these medications, tricyclic antidepressants, anticonvulsants, and antipsychotics may be used.[4,7,8,10,11] Psychotherapy, as monotherapy or combined with pharmacotherapy, has also been studied to treat GAD.[12] Psychotherapeutic approaches include cognitive behavioral therapy, psychodynamic therapy, and supportive therapy.[12]

Currently, there are two SNRIs approved by the FDA for the treatment of GAD – venlafaxine and, more recently, duloxetine. This article will review the efficacy of the SNRI duloxetine in the treatment of GAD.

Duloxetine

Pharmacodynamics

Duloxetine is a SNRI that is approved by the FDA for the treatment of MDD, neuropathic pain, fibromyalgia, and GAD.[13] Its mechanism of action is based upon reuptake inhibition of 5-HT and norepinephrine (NE) in the CNS.[14] A number of in vitro experiments show that duloxetine has good affinity for 5-HT and NE transporters, and is able to decrease 5-HT and NE uptake,[15–17] Other preclinical studies demonstrate the low affinity that duloxetine has for other transporters (DA, GABA)[18] and for other neuronal binding sites (monoamine receptor subtypes and ion channels).[15] In addition to in vitro studies, various in vivo techniques have been used to demonstrate duloxetine's inhibitory capabilities at 5-HT and NE transporters.[15,16]

There are also a number of clinical studies which demonstrate the ability of duloxetine to inhibit reuptake of NE and 5-HT.[14] Reuptake inhibition of 5-HT can be shown by the use of platelet 5-HT levels. Platelets have a similar mechanism of 5-HT reuptake to that found in the CNS, and therefore 5-HT levels in the blood depend on the extent of reuptake inhibition in platelets. Turcotte et al and Chalon et al have demonstrated this relationship by showing an increase in blood 5-HT levels using duloxetine doses of 20 mg daily to 120 mg daily.[19,20] Since there is no direct measure of NE reuptake inhibition, of NE activity is assessed by measuring the amount of NE and NE metabolites in the urine, cardiovascular effects NE reuptake inhibition, and by reduction of pain symptoms and adverse drug effects from NE reuptake inhibition.[14] Each of these methods has been used to successfully demonstrate the ability of duloxetine to inhibit NE reuptake.[14]

Pharmacokinetics

After a single 20.2 mg dose of oral duloxetine, the mean time to peak plasma concentration (C_{max}) is 6 hours.[21] During a dose escalation study, 8 subjects received duloxetine 20 mg twice daily, 30 mg twice daily then 40 mg twice daily. Steady state plasma concentrations were reached after 5 days and duloxetine has a mean half-life of 12.5 hours[22] (with a range of 8 to 17 hours);[13] thus duloxetine is a suitable candidate for once daily dosing. In the same study, duloxetine was shown to follow first-order absorption and elimination kinetics, and have a mean oral clearance of 114 L/hour, and mean apparent volume of distribution of 1943 L.[21] Absorption of duloxetine is unaffected by food,[13] which makes dosing convenient and aids medication adherence.

Duloxetine is greater than 90% plasma protein bound, so caution should be exercised when administered with other highly protein bound drugs such as warfarin or phenytoin.[13] It is extensively metabolized by the liver via CYP1A2 and CYP2D6[13] resulting in various metabolites, the most predominant of these being the glucuronide conjugate 4-hydroxy duloxetine.[21] Its metabolism by the cytochrome P450 system leads to the potential of certain drug interactions, as discussed in the next section. None of the duloxetine metabolites appear to be pharmacologically active.[13] Excretion occurs 72% via the kidneys and 19% via feces.[21]

Drug–drug interactions

Because of its metabolism by 1A2 and 2D6, there is a potential for drug interactions to take place between duloxetine and inhibitors, inducers, or substrates of these enzymes. When duloxetine 60 mg was co-administered with fluvoxamine 100 mg (a 1A2 inhibitor) as a single dose, the result was an approximately 6-fold increase in duloxetine AUC, 2.5-fold increase in C_{max}, and a 3-fold increase in half-life.[13] In another study, duloxetine 40 mg daily at steady state conditions was co-administered with paroxetine 20 mg (a potent 2D6 inhibitor). Pharmacokinetic analysis showed a 1.6-fold increase in both duloxetine AUC and C_{max}.[23] Duloxetine has been reported to have a small inhibitory effect on CYP1A2, but no effect on 2C9, 2C19 or 3A4.[13,24] It has, however, been shown to have a significant inhibitory effect on CYP2D6. Thirteen subjects each received desipramine 50 mg (a substrate for CYP2D6) after 21 days of duloxetine therapy. It was found that desipramine C_{max} had increased 1.7-fold, and AUC had increased 2.9-fold.[23] Another potential drug interaction involves the use of anticoagulants (owing to the small 1A2 inhibition).[25] Pharmacodynamic drug interactions may occur with MAOIs, and other serotonergic drugs, resulting in an increased risk of serotonin syndrome. An example of this involved an interaction between duloxetine and linezolid. Linezolid has been shown to be a nonselective inhibitor of monoamine oxidase.[26] It is recommended that patients be monitored closely if taking duloxetine concomitantly with any of these drug classes.[13]

Efficacy in GAD

A Medline search was made using the keywords duloxetine, Cymbalta®, generalized/generalised anxiety disorder, efficacy, and controlled trial. Five controlled trials for the use of duloxetine in GAD were found. The following section will summarize these trials.

Koponen et al carried out a multicenter, randomized, double blind, fixed-dose, placebo-controlled trial.[27] Study sites were located in the US, Europe, and South Africa. The study was a 9-week treatment phase followed by a 2-week discontinuation phase. All subjects participated in a pretreatment screening phase and washout period, and a 1-week single-blind placebo lead in phase. Subjects were diagnosed with GAD by a psychiatrist via the use of the Mini-International Neuropsychiatric Interview (MINI) and according to DSM-IV criteria. Subjects were excluded from the trial if the patient suffered from significant comorbidities or other mental disorders such as a recent diagnosis of MDD, substance abuse, post-traumatic stress disorder (PTSD), panic disorder, eating disorder, bipolar, obsessive compulsive disorder, or psychosis. Subjects were randomly assigned one of two active treatment groups: 60 mg duloxetine daily, or 120 mg duloxetine daily, along with a placebo group. The mean total Hamilton Rating Scale for Anxiety (HAM-A) scores at baseline were approximately 25 in all 3 groups, indicating moderately severe GAD.

The primary efficacy outcome measure was defined as a >50% reduction in total HAM-A score from baseline, and sustained improvement rates were defined as a >30% reduction in total HAM-A score from baseline to the last visit. Remission was defined as a <7 HAM-A total score at endpoint. Secondary outcome measures were scores on the HAM-A psychic factor, the HAM-A somatic factor, the patient reported Hospital Anxiety and Depression Scale (HADS), the Clinical Global Impressions-Improvement scale (CGI-I), the Patient Global Impressions-Improvement scale (PGI-I), and the Sheehan Disability Scale (used to rate social, family, and work impairment).

Both treatment arms reported a significantly greater decrease in total HAM-A score as compared to placebo. The mean change from baseline was −12.8 in the 60 mg group, −12.5 in the 120 mg group, and −8.38 in the placebo group ($P < 0.001$ for both groups vs placebo). (Standard deviations were not reported). This corresponded to a mean decrease in total HAM-A score of 49% in duloxetine treated patients. A response was achieved by 58% of the duloxetine 60 mg group, 56% of the duloxetine 120 mg group, and 31% of the placebo group ($P < 0.001$ both groups vs placebo), and remission was achieved by 31%, 38%, and 19% of the duloxetine 60 mg, 120 mg, and placebo groups, respectively ($P < 0.01$ for duloxetine 60 mg vs placebo; $P < 0.001$ for duloxetine 120 mg vs placebo). The duloxetine groups also had significantly greater sustained improvement rates as compared with the placebo group −64% and 67% for the 60 mg and 120 mg groups respectively, vs 43% for placebo ($P < 0.001$ both groups vs placebo). Secondary outcome measures also showed a greater improvement in the duloxetine groups over the placebo group (Table 2).

A similar study was completed by Rynn et al[28] and with the same primary and secondary endpoints as Koponen et al.[27] However, this study was conducted at sites exclusively in the US and consisted of a 10 week-long therapy phase rather than 9 weeks. Also, this study involved a titrated duloxetine dose as opposed to a fixed dose. All subjects participated in a pre-treatment screening phase and washout period, and a 1-week, single-blind placebo lead in phase. Subjects

Table 2 Efficacy and demographic data

	Nicolini et al 2009[30]				Koponen et al 2007[27]			Rynn et al 2008[28]		Hartford et al 2007[29]		
Demographic data												
Male	249 (42.9%)				165 (32.3%)			125 (38.3%)		182 (37.4%)		
Female	332 (57.1%)				348 (67.8%)			202 (61.7%)		305 (62.6%)		
Mean age (years)	42.8				43.8			41.6		40.8		
Time frame	**10-week therapy phase**				**9-week therapy phase**			**10-week therapy phase**		**10-week therapy phase**		
Regimen	DLX	DLX	VEN XR	Placebo	DLX	DLX	Placebo	DLX	Placebo	DLX	VEN XR	Placebo
DLX	20 mg/day	60–120 mg/day	75–225 mg/day	N = 163	60 mg/day	120 mg/day	N = 175	60–120 mg/day	N = 159	60–120 mg/day	75–225 mg/day	N = 161
VEN	N = 83	N = 151	N = 158		N = 168	N = 170		N = 168		n = 162	N = 164	
All *P* results are significant vs placebo unless stated otherwise												
Racial origin, N (%)					163 (97.0)	169 (99.4)	173 (98.9)	134 (79.8)	124 (78.0)	108 (67.1)	118 (72.0)	113 (70.2)
Caucasian	392 (67.5)				0	0	1 (0.6)	7 (4.2)	12 (7.6)	14 (8.7)	23 (14.0)	19 (11.8)
Hispanic	128 (22.0)				1 (0.6)	1 (0.6)	1 (0.6)	20 (11.9)	21 (13)	34 (21.1)	19 (11.6)	25 (15.5)
African American	–				4 (2.4)	0	0	7 (4.1)	2 (1.3)	–	–	–
Asian	–				–	–	–	–	–	5 (3.1)	4 (2.4)	4 (2.5)
Other	61 (10.5)											
HAMA baseline score	27.4				25.0	25.2	25.8	22.6	23.5	25.6	24.9	25.0
Primary measures												
HAMA total score (mean change)	−14.7	−15.3	−15.5	−11.6	−12.8	−12.5	−8.38	−8.12	−5.89	−11.80	−12.40	−9.19
Secondary measures												
HAMA psychic factor score (mean change)	−8.1	−8.7	−8.6	−6.0	−7.57	−7.15	−4.53	−5.33	−3.33	−7.01	−7.57	−5.13
HAMA somatic factor score (mean change)	−6.6*	−6.6	−7.0	−5.5	−5.19	−5.33	−3.82	−2.81*	−2.54*	−4.74*	−4.84*	−4.08*
HAMA anxious mood score (mean change)	–	–	–	–	−1.51	−1.51	−0.85	−0.98	−0.64	−1.40	−1.60	−1.00
HAMA tension score (mean change)	–	–	–	–	−1.37	−1.35	−0.82	−0.98	−0.67	−1.37	−1.42	−1.03
CGI-I (mean rating at endpoint)	–	–	–	–	2.33	2.38	2.94	2.68	2.97	2.39	2.30	2.80
PGI-I (mean rating at endpoint)	–	–	–	–	2.58	2.53	3.17	2.88	3.20	2.60	2.65	3.06

HADS Anxiety subscale (mean change)	−7.0	−7.7	−6.9	−4.9	−5.80	−5.82	−3.42	−3.92	−2.08	−6.22	−6.46	−4.04
HADS Depression subscale (mean change)	−3.3	−3.5	−3.6	−1.9	−3.47	−3.32	−1.75	−2.36	−1.58	−3.91	−3.50	−2.14
SDS global functional impairment score (mean change)	−8.5	−8.9	−9.1	−6.2	–	–	–	–	–	−8.03	−7.97	−5.42
Response rate	60%	65%	61%	42%	58%	56%	31%	40%	32%	47%	54%	37%
Remission rate	42%	44%	44%	20%	31%	38%	19%	28%	23%	23%*	30%	19%

*Outcome measures were not significant vs placebo ($P > 0.05$)
Abbreviations: DLX, duloxetine; VEN, venlafaxine; HAMA, Hamilton Anxiety Rating Scale; CGI-I, Clinical Global Impressions Scale; PGI-I, Patient Global Impressions-Improvement scale; HADS, Hospital Anxiety and Depression Scale; SDS, Sheenan Disability Scale.

were randomly assigned to either an active treatment group, dosed at 60 to 120 mg duloxetine daily, or a placebo group. Patients began taking 60 mg duloxetine daily. After 2 weeks of treatment, and if tolerated, this dose was titrated upwards (in 30-mg increments) to a maximum of 120 mg daily, if the subject's CGI-I rating was >3 (signifying little, or no improvement). Baseline total HAM-A scores were approximately 22.6 ± 7.4 for the duloxetine group, and 23.5 ± 7.9 for the placebo group.

The mean dose taken by the active duloxetine group was 101.94 mg/day (18.23% at 60 mg/day, 23.66% at 90 mg/day, and 58.06% at 120 mg/day). The duloxetine treatment arm experienced a greater decrease in total HAM-A score compared to placebo where the mean change from baseline was −8.12 vs −5.89 for placebo ($P = 0.023$) (standard deviations were not reported). This corresponded to a mean decrease in total HAM-A score of 36% in duloxetine-treated patients. A response was achieved by 40% of the duloxetine group, and 32% of the placebo group ($P < 0.05$), and remission was achieved by 28% and 23% of the duloxetine and placebo groups, respectively (NS, $P = 0.27$). Sustained improvement rates were significantly greater for the duloxetine group compared to placebo, being 43.7% and 32%, respectively ($P < 0.05$). Secondary outcome measures also showed a greater improvement in the duloxetine group over the placebo group.

Two studies carried out by Hartford et al[29] and Nicolini et al[30] looked at the efficacy of duloxetine and venlafaxine XR (venlafaxine extended release) for the treatment of GAD. Individually, these studies were not powered to draw a direct comparison between duloxetine and venlafaxine XR, but when pooled together, a noninferiority analysis could be done. Both studies were multicenter, randomized, double-blind, parallel-group, placebo-controlled studies conducted at various sites in North and South America, Europe, Australia, Russia, and Taiwan. Both consisted of a 10-week treatment period where subjects were randomized to receive either duloxetine, venlafaxine XR or placebo. Subject diagnosis with GAD, primary and secondary outcomes, and exclusion/inclusion criteria were the same as for the Koponen[27] and Rynn[28] studies.

For Hartford et al subjects were randomly assigned to receive either titration-based duloxetine 60 to 120 mg/day, venlafaxine XR 75 to 225 mg/day, or placebo. For Nicolini et al subjects were randomized to receive duloxetine 20 mg/day, duloxetine 60 to 120 mg/day, venlafaxine XR 75 to 225 mg/day, or placebo (n = 170) (the duloxetine 20 mg daily dose was fixed and was included to satisfy

European regulatory requirements). For both studies, the duloxetine group daily dose was titrated in 30-mg increments to a maximum of 120 mg daily, if tolerated. The venlafaxine group's doses were titrated from 75 mg daily up to a maximum of 225 mg daily, if tolerated. Doses were increased if there was no improvement in CGI-I score (ie, ≥3).

At endpoint, the mean duloxetine doses being taken were 107.73 mg/day for Hartford et al and 90 mg/day for Nicolini et al. The duloxetine treatment arms experienced a greater decrease in total HAM-A score compared to placebo. The mean changes from baseline in the duloxetine 60 to 120 mg groups were −11.8 ± 0.69(SE) for the Hartford et al study, and −15.3 ± 0.7(SE) for the Nicolini et al study, which corresponds to mean decreases in HAM-A of 46% and 55%, respectively. The duloxetine 20 mg group from the Nicolini et al study saw a HAM-A decrease of 14.7 ± 1.0 (SE) corresponding to a mean decrease of 45%. All changes were statistically significant vs placebo. Efficacy and demographic data for the 4 studies discussed previously is summarized in Table 2.

In addition to the 4 acute clinical trials, a relapse prevention study of duloxetine in GAD was conducted.[31] The study determined the relapse rate of GAD after discontinuation of duloxetine, and was a randomized, double blind, placebo-controlled trial, conducted at sites throughout the US and Europe. It consisted of a 26-week open label phase where 887 patients were enrolled to take duloxetine 60 to 120 mg daily. This was done in a flexible dosing manner, whereby doses were increased from 60 mg to 120 mg daily if patients were non responsive (defined as a CGI-I ≤ 3) and if medication could be tolerated. If subjects were responsive to their medication (defined as a ≥50% reduction in HAM-A total score from baseline) they were randomized into the double-blind, placebo-controlled continuation phase of the study. Subjects who were randomized to receive placebo had their duloxetine dose tapered over a 2-week period. The primary efficacy measure for this trial was time to relapse, with relapse defined by a ≥2 point increase on the CGI-S scale and a score of ≥4. Secondary measures were similar to the previous studies, and included HAM-A total score, HADS, and SDS. Out of the 887 subjects in the open label phase, 429 were randomized to take part in the continuation phase. Reasons for subject discontinuation included inadequate response during open label phase (9.7%), adverse events (AEs) (13.6%) and patient decision (12%). Subjects remaining were assigned to either duloxetine (continued at the same dose as during the open-label phase) or placebo for 26 weeks.

Results showed that duloxetine was superior to placebo in preventing relapse of GAD over the 26-week period. Relapse criteria was met by 13.7% of the duloxetine group compared to 41.8% of the placebo group ($P \leq 0.001$), and the mean change in HAM-A score from baseline was 7.5 ± 0.6 (SE) for the placebo group vs 1.6 ± 0.6 (SE) for the active group ($P \leq 0.001$). For the patients who did relapse, those treated with placebo relapsed at an earlier time period than those treated with duloxetine ($P \leq 0.001$).

Special patient populations

Using pooled data from previous studies the use of duloxetine was analyzed in specific patient populations. An analysis of duloxetine efficacy in treating GAD patients with clinically significant pain symptoms was conducted by Russell et al[32] Data was pooled from the studies completed by Koponen et al[27] and Rynn et al[28] In both studies, pain was assessed using visual analogue scales (VAS) and statistical analysis was conducted in patients with a VAS score > 30. This score was considered to be the point at which patients with little or no bodily pain was distinguishable from those with notable pain. Based upon these criteria, 44% of patients were identified in the intent to treat (ITT) group. Results of the analysis showed a significant decrease in overall VAS score for the duloxetine treated patients compared to placebo (mean change from baseline 48.7% vs 31.3%; $P < 0.001$). There was also a direct correlation between reduction in VAS score and improvement in CGI-I scores. Patients with a final CGI-I score of 1 (max. improvement) had a mean reduction of 77.4% in total VAS score. Likewise, this was shown in the relationship between VAS score and PGI-I score, with patients having a final PGI-I score of 1 (maximum improvement) having a mean reduction in VAS score of 76.4%. Given that GAD patients with pain have more severe symptoms, this analysis shows that duloxetine can deliver significant reductions in pain in patients with anxiety.

Another meta-analysis study assessed duloxetine's use in elderly patients with GAD. Clearly, pharmacotherapy in this population carries with it treatment concerns including polypharmacy, changes in drug metabolism, and other geriatric conditions such as Alzheimers disease. Davidson et al[33] pooled data from four studies that were discussed previously.[27–30] Out of the 1491 patients, data were taken from patients over 65 years of age, where 45 patients in the duloxetine group and 28 in the placebo group were found (73 patients in total equaling 4.9% of sample). All patient data were used to evaluate safety, and patients who completed

at least one post baseline measurement were included in the efficacy analysis. The analysis showed that a significant reduction in HAM-A total score for patients treated with duloxetine occurred compared to placebo (10.1 vs 5.9; $P = 0.029$). Other significant improvements were noted for the HAM-A-psychic factor, HADS anxiety and depression scales. However, significant differences between CGI-I or PGI-I scores compared to placebo, or rates of remission and sustained improvement were not found (24% vs 7%, $P = 0.053$ and 62% vs 36%, $P = 0.05$, respectively). The study authors concluded the lack of statistical significance was likely due to the relatively small number of study subjects involved in the analysis.

Safety and tolerability

In general, duloxetine was safe and well tolerated with AEs being mild to moderate in severity. The most common AE was nausea (experienced by about 30% to 40% of duloxetine patients) and it was the most frequent reason for study discontinuation due to an AE. Other AEs that occurred more often than placebo were constipation, dry mouth, somnolence, decreased appetite, insomnia, decreased libido, and yawning, although these were regarded as mild and occurred at a relatively low rate.[27–31] Discontinuation rates due to all AEs for duloxetine patients varied from 2.4% to 20.2%.[27,28]

Serious adverse events (SAEs) occurred at a low frequency, and consisted of upper abdominal pain, vomiting, renal cell carcinoma, alcoholism, depression, self-mutilation,[29]anxiety, atrial fibrillation, back pain, chest pain, migraine,[28] myocardial infarction, erysipelas,[27] bronchitis, diarrhea, worsening of GAD, and a ruptured tendon.[31] There was no significant difference in SAEs between active and placebo groups. There were 2 fatalities (cerebral hemorrhage and suicide), although these were determined to be unrelated to study drug.[31] Discontinuation emergent adverse events occurred at a rate of 19.9% to 22.1%, dizziness being the most prominent.[27–31]

In the analysis examining duloxetine in GAD patients with significant pain symptoms, safety and tolerability were not analyzed statistically. For duloxetine use in the elderly population, adverse event rates were similar to those observed among the general population.[33] Nausea was the most experienced AE, 30% of duloxetine-treated patients experiencing nausea vs 7.1% for placebo ($P = 0.023$). In addition, duloxetine-treated patients lost more weight than the placebo group (−1.1 kg vs 0.0 kg, $P = 0.018$). There were no other significant differences between the 2 groups in AEs or reported lab values. A list of AEs and their frequency is shown in Table 3.

Discussion

Duloxetine is approved for treatment for GAD in doses of 30 mg to 120 mg daily. Studies have indicated that duloxetine can reduce GAD symptoms. Duloxetine showed significant reductions in HAM-A scores and other measures of GAD. Duloxetine also appears to be relatively well tolerated with AEs being relatively mild and comparable to other those for reuptake inhibitors. Interestingly, in one study,[30] a 20 mg dose of duloxetine appeared to offer similar efficacy to the higher doses used (60 to 120 mg). It may be worthwhile conducting a dose-response study to determine if GAD could be successfully treated with duloxetine at doses lower than those currently used, or for clinicians to initiate treatment at 20 mg daily for 4 to 6 weeks before titrating to higher doses. This may help improve patient adherence by reducing the frequency and severity of AEs.

Only one noninferiority comparator study (against venlafaxine XR) has been done, therefore it is difficult to assess whether duloxetine is a more appropriate treatment option other compared with more established and less costly options. Allgulander et al[34] analyzed duloxetine vs venlafaxine using data from 2 previous studies.[29,30] This analysis found a HAM-A score decrease of 3.8 for duloxetine over placebo and of 3.6 for venlafaxine over placebo, which confirmed that duloxetine met criteria for noninferiority against venlafaxine XR. In addition to the efficacy outcome, it was observed that there was no significant difference between the duloxetine and venlafaxine XR groups in the number of patients who discontinued the study because of AEs, or in rate of discontinuation for any specific AE. Both medications had similar tolerability and safety profiles, except for nausea and yawning which occurred at significantly higher rates in duloxetine-treated patients (nausea rates were 26.9% for duloxetine and 20.1% for venlafaxine XR [$P < 0.05$], yawning data not reported).

First-line treatment options available for treating GAD involve the use of SSRIs, SNRIs, benzodiazepines, and buspirone.[2] Benzodiazepines are particularly effective anxiolytics; however, their lack of antidepressant effect and side effect profile make them undesirable for long-term use. Buspirone has good anxiolytic properties, but its negligible antidepressant effect makes it unsuitable for treating the comorbid depression that is highly prevalent in the GAD patient population. Antidepressants such as the SSRI paroxetine, and the SNRI venlafaxine have been shown to be

Table 3 Safety and tolerability data

	Nicolini et al 2009[30]				Koponen et al 2007			Rynn et al 2006		Hartford et al 2007[29]			Davidson et al 2008[31]
Time frame	**10-week therapy phase**				**9-week therapy phase**			**10-week therapy phase**		**10-week therapy phase**			**26-week open label phase**
DLX (dose in mg/day)	DLX	DLX	VEN XR	Placebo	DLX (60)	DLX	Placebo	DLX	Placebo	DLX	Venl XR	Placebo	DLX
VEN (dose in mg/day)	(20)	(60–120)	(75–225)	N = 163	N = 168	(120)	N = 175	(60–120)	N = 159	(60–120)	(75–225)	N = 161	(60–120)
All *P* results are significant vs placebo unless stated otherwise	N = 83	N = 151	N = 158			N = 170		N = 168		N = 162	N = 164		N = 216
TEA													
Any adverse effect								140 (83.3)	116 (73)	136 (84)	140 (85.4)	117 (72.7)	
Nausea	(18)†	(23)†	(17)*†	(10)†	(41.7)	(43.6)	(7.4)	62 (36.9)	16 (10.1)	51 (31.5)	38 (23.2)	22 (13.7)	(28.3)
Constipation	(7)*†	(12)†	(8)*†	(4)†				14 (8.3)	5 (3.1)	23 (14.2)	22 (13.4)	7 (4.3)	(12.5)
Decreased libido								9 (5.4)*	4 (2.5)	11 (6.8)	5 (3)*	1 (0.6)	(5.4)
Diarrhea													(14.2)
Dizziness								28 (16.7)	11 (6.9)				(13.4)
Dry mouth	(7)†	(13)†	(8)†	(3)†				11 (6.5)	3 (1.9)	19 (11.7)*	29 (17.7)	10 (6.2	(14.3)
Fatigue	(7)*†	(8)†	(6)*†	(3)†				20 (11.9)*	9 (5.7)	12 (7.4)*	19 (11.6)	6 (3.7)	(11.5)
Headache													(18.7)
Somnolence	(3)*†	(8)†	(4)*†	(2)†				20 (11.9)	1 (0.6)	19 (11.7)	22 (13.4)	6 (3.7)	(8.2)
Insomnia								11 (6.5)*	5 (3.1)	12 (7.4)	15 (9.1)	3 (1.9)	(9.8)
Tremor	0*†	(4)*†	(3)*†	(1)†				9 (5.4)	1 (0.6)				
Palpitations													
Decreased appetite										16 (9.9)	14 (8.5)	4 (2.5)	(6.1)
Yawning										12 (7.4)	5 (3.0)	0	
Hyperhidrosis	(5)*†	(9)†	(6)†	(1)†									(10.0)
Upper respiratory tract infection													(5.5)
Vomiting													(5.4)
TEA resulting in study discontinuation	(4.8)*†	(12.7)*†	(11.8)*†	(8.8)†	(6.0)	(2.4)*	0	(20.2)	(8.2)	(14.2)	(11)	(1.9)	(13.6)
SAE								4*	1	3*	2*		11
DEAE					(31.1)	(29.8)	(16.2)	(22.1)*	(17.3)*	18 (19.4)*	28 (26.9)	(15.8)	
Dizziness													(9.9)

Note: Data are presented as N (%).
*Results are not statistically significant vs placebo significant ($P \leq 0.05$).
†Data are approximate values.
Abbreviations: DLX, duloxetine; VEN, venlafaxine; TEA, treatment emergent adverse event; SAE, serious adverse events; DEAE, discontinuation emergent adverse events.

both effective anxiolytics and antidepressants, making them good options for the GAD patient.[35] Duloxetine, being a SNRI, is one more option at hand from the array of medications available in the SSRI/SNRI class. However, at this time it should be noted there are no direct comparator studies between these different drug classes, thus it is difficult to ascertain the superiority of one treatment over another. Whether clinicians choose to begin treating GAD with an SNRI, SSRI, or other class of medication will ultimately come down to patient history, tolerability to the medication, clinician experiences, and cost.[36]

It should be noted that all five efficacy studies were sponsored by Eli Lilly, who developed and market duloxetine (Cymbalta®).

Disclosure

The authors declare no conflicts of interest.

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