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Profile of Adverse Events with Duloxetine Treatment

A Pooled Analysis of Placebo-Controlled Studies

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Abstract

Background: The serotonin and noradrenaline (norepinephrine) reuptake inhibitor duloxetine has been approved in the US and elsewhere for a number of indications, including psychiatric illnesses and chronic pain conditions. Because the patient populations are diverse within these approved indications, and duloxetine is not yet approved for treatment of other conditions, we wanted to determine if adverse event profiles would differ among patients being treated for these various conditions.

Objective: To provide detailed information on the adverse events associated with duloxetine and to identify differences in the adverse event profile between treatment indications and patient demographic subgroups.

Methods: Data were analysed from all placebo-controlled trials of duloxetine completed as of December 2008. The 52 studies included 17 822 patients (duloxetine n = 10 326; placebo n = 7496) with major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, osteoarthritis knee pain (OAKP), chronic lower back pain and lower urinary tract disorders. The main outcome measures were rates of treatment-emergent adverse events (TEAEs) and adverse events reported as the reason for discontinuation.

Results: The overall TEAE rate was 57.2% for placebo-treated patients and 72.4% for duloxetine-treated patients ($p \leq 0.001$). Patients with OAKP had the lowest TEAE rate (placebo 36.7% vs duloxetine 50.2%, $p \leq 0.01$), while patients with fibromyalgia had the highest rate (placebo 80.0% vs duloxetine 89.0%, $p \leq 0.001$). The most common TEAE for all indications was nausea (placebo 7.2% vs duloxetine 23.4%, $p \leq 0.001$), which was predominantly mild to moderate in severity. No statistically significant treatment-by-subgroup interactions for age were found between placebo and duloxetine treatment for the most common TEAEs. The rates of duloxetine-associated dry mouth and fatigue were greater in women than in men (13.1% vs 10.4%, interaction

p = 0.004; and 9.4% vs 7.6%, interaction p = 0.03, respectively). Duloxetine-associated dry mouth incidence was higher in Caucasians than non-Caucasians (13.2%, 11.0%, interaction p = 0.04).

Conclusions: Duloxetine treatment is associated with significantly higher rates of common TEAEs versus placebo, regardless of indication or demographic subgroup. Differences across indications are likely to be attributable to the underlying condition rather than duloxetine, as suggested by the similar trends observed in placebo- and duloxetine-treated patients.

Background

Duloxetine (duloxetine hydrochloride) is a relatively balanced selective serotonin and noradrenaline (norepinephrine) reuptake inhibitor (SNRI)[1] that is approved in the US for the treatment of major depressive disorder (MDD) and generalized anxiety disorder (GAD), and the management of diabetic peripheral neuropathic pain (DPNP) and fibromyalgia.[2] In Europe, duloxetine is approved for the treatment of MDD, GAD, DPNP and stress urinary incontinence (SUI) in women.[3]

The efficacy of duloxetine in the treatment of MDD, DPNP, GAD, fibromyalgia and SUI is dependent on its actions on the CNS via inhibition of serotonin and noradrenaline reuptake and the resulting increase in extracellular serotonin and noradrenaline levels, which potentiate the effects of these neurotransmitters.[4] The underlying neurobiology of MDD and GAD suggests involvement of one or more neurotransmitter systems, including serotonin, noradrenaline and GABA transmission.[5,6] Multiple mechanisms, including disinhibition of serotonin and noradrenaline in endogenous pain inhibitory pathways, are implicated in the physiopathology of persistent pain.[7] Serotonin and noradrenaline act as pain modulators in the descending pathways of the spinal cord[8-10] and enhancement of this activity via medications that inhibit the reuptake of serotonin and noradrenaline in the CNS may play an important role in analgesic efficacy.[11]

Safety information on duloxetine in the treatment of MDD, GAD, DPNP, fibromyalgia and lower urinary track disorders (LUTD), including SUI, has been obtained from individual clinical trials;[12-15] however, there have been two recent pooled analyses[16,17] in which the safety and tolerability of duloxetine were evaluated. In a pooled analysis of 64 studies of duloxetine, Gahimer et al.[16] reported an incidence of treatment-emergent adverse events (TEAEs) of 75%, with most being mild to moderate in severity and with an early onset; however, that study did not include placebo-treated patients, therefore it was not possible to compare the rates of TEAEs associated with placebo and duloxetine in order to assess the effect of the drug. In 2007, the cardiovascular safety of duloxetine from 42 placebo-controlled studies was analysed.[17] Duloxetine treatment did not increase risk of sustained blood pressure elevation and although statistically significant changes occurred in heart rate, these were not considered clinically relevant.

Duloxetine has regulatory approval for the treatment of multiple conditions; therefore, primary-care physicians can prescribe duloxetine to a broad range of patients with different demographic characteristics such as age, sex and race. Thus, comprehensive analyses of the adverse event profile of duloxetine treatment compared with placebo by indication as well as by age, sex and race will be helpful to assess if any differences occur in these patient populations. This would aid primary-care physicians in better understanding the adverse event profile of duloxetine.

In this pooled analysis, we evaluated TEAEs in patients included in 52 placebo-controlled trials of duloxetine for the treatment of MDD, GAD, DPNP, fibromyalgia, LUTD, osteoarthritis knee pain (OAKP) and chronic lower back pain (CLBP), in order to provide complete and detailed information of the TEAE profile

of duloxetine by indication, dose and patient demographics.

Methods

Characteristics of Included Studies

To evaluate the tolerability of duloxetine, we used the integrated safety database to obtain data from all randomized, double-blind, placebo-controlled, multicentre trials of duloxetine completed as of December 2008, regardless of whether the study had been published (table I). We excluded two relapse prevention studies that had open-label run-ins lasting at least 3 months. A total of 52 studies, with data from 17 822 patients (placebo n = 7496; duloxetine n = 10 326), were analysed to obtain information on the profile of adverse events associated with duloxetine across all approved treatment indications, as well as indications under clinical investigation, including MDD (16 studies), GAD (4 studies), DPNP (4 studies), fibromyalgia (4 studies), OAKP (2 studies), CLBP (2 studies) and LUTD (20 studies). All patients were at least 18 years of age. The duration of the treatment phase was 3 months or less in most studies (n = 44) and the dosages of duloxetine administered ranged between 5 and 120 mg/day. The majority of patients received 60, 80 or 120 mg/day. Dosing schedules were fixed or flexible (i.e. could be adjusted to provide improved efficacy or tolerability).

Ethical Considerations

National or institutional review boards at each study site approved the protocols. All studies were conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from each participant prior to entrance into a study.

Evaluated Data

Duloxetine safety was assessed by analysing the frequency and maximum severity of adverse events, and the onset and duration of these events. An adverse effect was considered treatment-emergent if it was a new symptom or worsening of a pre-existing symptom compared with that reported at baseline. Common TEAEs are defined as adverse effects that were experienced by 5% or more of duloxetine-treated patients.

The type and severity of adverse events were obtained by clinical observation, patient-reported questionnaires and source document review, although only adverse events spontaneously reported by the patients were used for the following analyses. Preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA® version 11.0) were used to summarize the TEAEs from the integrated safety database. These data were analysed by age (<65 or ≥65 years), sex, race, duloxetine dose and indication for duloxetine treatment. For flexible dosing studies (15 of 52), given the variety of dose escalation schemes, the highest dose was considered the most appropriate for analysis. The severity of adverse events was reported by patients and registered as mild, moderate or severe. The maximum severity was used in the analysis if one event was reported multiple times. Discontinuations due to adverse events were summarized and also analysed by duloxetine dose.

Statistical Methods

The rates of TEAEs were analysed using the Cochran-Mantel-Haenszel test controlling for study to determine the general association between TEAE and treatment groups. Treatment-by-subgroup interactions were assessed using logistic regression; the model terms included the study, treatment, subgroup and treatment by subgroup. Within-subgroup comparisons were carried out using Fisher's exact test. The median duration of TEAEs was estimated using the Kaplan-Meier method. Statistical hypotheses were tested at a significance level of 0.05, except for tests of interactions, which were tested at a level of 0.1.

Results

Patient Demographics

A total of 17 822 patients were randomized to receive either placebo (n = 7496) or duloxetine (n = 10 326). The majority of patients were female (81.3%), Caucasian (83.8%) and had a mean age of 51.4 years (range 18–91 years). The characteristics

Table I. Summary of the 52 randomized, double-blind, placebo-controlled, multicentre studies (completed as of December 2008) included in the analyses

Study identifier	Study phase	Placebo (n)	Duloxetine [n (dosage; mg/day)]	Treatment duration (wk)	Primary disclosure
Chronic lower back pain					
HMEN	III	121	115 (60–120)	13	Skljarevski et al.[18] (in press)
HMEO	III	117	287 (20, 60, 120)	13	Skljarevski et al.[19] (2009)
Osteoarthritis knee pain					
HMEP	III	120	111 (60–120)	13	Chappell et al.[20] (2009)
HMFG	III	128	128 (60–120)	13	NCT00433290
Major depressive disorder					
HMAG	Ib/II	52	53 (10–30)	10	CT Registry ID #1124
HMAH	II	88	89 (20–30)	10	CT Registry ID #1125
HMAI	II	126	390 (5, 10, 20)	8	CT Registry ID #1126
HMAQ (a)	II	70	70 (40–120)	8	Goldstein et al.[21] (2002)
HMAQ (b)[a]	II	75	82 (40–120)	8	Nemeroff et al.[22] (2002)
HMAT (a)[b]	III	90	175 (40, 80)	8	Nemeroff et al.[22] (2002)
HMAT (b)[c]	III	89	177 (40, 80)	8	Goldstein et al.[23] (2004)
HMAY (a)[d]	III	93	188 (80, 120)	8	Detke et al.[24] (2004)
HMAY (b)[e]	III	99	196 (80, 120)	8	Perahia et al.[25] (2006)
HMBH (a)	III	122	123 (60)	9	Detke et al.[26] (2002)
HMBH (b)	III	139	128 (60)	9	Detke et al.[27] (2002)
HMBV	IV	104	207 (60)	8	Raskin et al.[28] (2007)
HMCB	IIIb	141	141 (60)	7	Brannan et al.[29] (2005)
HMCR[f]	IIIb	137	273 (60–120)	8	Nierenberg et al.[30] (2007)
HMDH	IIIb	165	162 (60)	8	Brecht et al.[31] (2007)
HQAC	II	35	35 (60, 120)	4	Mundt et al.[32] (2007)
Diabetic peripheral neuropathic pain					
HMAV (a)	III	108	226 (60–120)	12	Wernicke et al.[33] (2006)
HMAV (b)	III	116	232 (60, 120)	12	Raskin et al.[15] (2005)
HMAW	II	115	342 (20, 60, 120)	12	Goldstein et al.[34] (2005)
HMEQ	III	109	106 (60, 120)	12	NCT00408993
Generalized anxiety disorder					
HMBR	III	175	338 (60, 120)	9	Koponen et al.[35] (2007)
HMDT	III	159	168 (60, 120)	10	Rynn et al.[36] (2008)
HMDU	III	161	162 (60, 120)	10	Hartford et al.[37] (2007)
HMDW[g]	III	170	242 (20, 60–120)	10	Nicolini et al.[38] (2009)

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Table I. Contd

Study identifier	Study phase	Placebo (n)	Duloxetine [n (dosage; mg/day)]	Treatment duration (wk)	Primary disclosure
Fibromyalgia					
HMBO	II	103	104 (120)	12	Arnold et al.[39] (2004)
HMCA	III	120	234 (60, 120)	12	Arnold et al.[12] (2005)
HMCJ	III	144	376 (20, 60, 120)	28	Russell et al.[40] (2008)
HMEF	III	168	162 (60, 120)	27	Chappell et al.[41] (2008)
Lower urinary tract disorders					
SAAA	II	37	55 (20)	3	Unpublished
SAAB	II	67	221 (20, 30, 40)	6	Skinner et al.[42] (2004)
SAAH	II	16	16 (40)	1	Steers et al.[43] (2007)
SAAI	II	44	47 (30, 40)	8	Viktrup et al.[44] (2004, part of pooled analysis)
SAAL	II	16	34 (30, 40)	9	Steers et al.[43] (2007)
SAAW	II	138	415 (20, 40, 80)	12	Norton et al.[45] (2002)
SBAB	II	31	34 (80)	4	Cardozo et al.[46] (2004)
SBAF	II	97	104 (80)	12	Ghoniem et al.[47] 2005)
SBAM	II	54	55 (80,120)	8	Cardozo et al.[46] (2004)
SBAT	III	247	247 (80)	12	Van Kerrebroeck et al.[48] (2004)
SBAV	III	339	344 (80)	12	Dmochowski et al.[49] (2003)
SBAX	III	231	227 (80)	12	Millard et al.[50] (2004)
SBBA	III	227	224 (80)	36	Kinchen et al.[51] (2005)
SBBL	II	153	153 (80–120)	12	Steers et al.[43] (2007)
SBBO	IIIb	288	300 (80)	8	Bent et al.[52] (2008)
SBBR	IIIb	120	396 (80)	8	Castro-Diaz et al.[53] (2007)
SBBT	III	61	60 (80)	8	NCT00475358
SBBU	III	60	61 (80)	8	Mah et al.[54] (2006)
SBCC	IIIb	1380	1378 (80)	6	Lin et al.[55] (2008)
SBCM	IV	131	134 (80)	12	Schagen van Leeuwen et al.[56] (2008)

a Fluoxetine 20 mg/day active control (n = 37).

b Paroxetine 20 mg/day active control (n = 89).

c Paroxetine 20 mg/day active control (n = 87).

d Paroxetine 20 mg/day active control (n = 86).

e Paroxetine 20 mg/day active control (n = 97).

f Escitalopram 10 mg, 20 mg active control (n = 274).

g Venlafaxine 75–225 mg/day active control (n = 169).

CT Registry = Clinical Trials Registry at lillytrials.com; **NCT** = National Clinical Trial identification number provided to aid in the location of unpublished studies.

of the pooled patient populations are shown in table II.

Overall Rates of Treatment-Emergent Adverse Events (TEAEs)

The proportion of patients having at least one TEAE in the entire pooled patient population was 57.2% for placebo- and 72.4% for duloxetine-treated patients ($p \leq 0.001$; table III). Nausea was the most frequently reported TEAE in the duloxetine group (23.4%) followed by dry mouth (12.6%), headache (12.0%) and constipation (10.1%). In the placebo group, these same TEAEs had rates of 7.2%, 3.8%, 9.4% and 3.1%, respectively. The majority of common TEAEs experienced by patients treated with duloxetine were mild or moderate in severity. Moderate and severe TEAEs occurred in greater proportions of duloxetine-treated patients than placebo-treated patients (moderate: duloxetine 33.5%, placebo 26.0%, $p \leq 0.001$; severe: duloxetine 15.4%, placebo 9.3%, $p \leq 0.001$). The proportion of patients who experienced mild TEAEs was not significantly different between the duloxetine and placebo treatment groups (duloxetine 23.5%, placebo 21.9%, $p = 0.058$). The proportion of patients who experienced mild headache was also similar in the duloxetine and placebo treatment groups. The severity of the most common TEAEs is shown in figure 1.

TEAEs Across Indications

TEAEs occurred significantly more frequently in duloxetine-treated patients compared with placebo-treated patients for all indications ($p \leq 0.05$ vs placebo; table III). The proportion of patients having at least one TEAE was highest among patients with fibromyalgia for both the placebo and duloxetine treatment groups (80.0% and 89.0%, respectively; $p \leq 0.001$) and was lowest in patients with OAKP (placebo 36.7%, duloxetine 50.2%, $p = 0.003$). Nausea was the most common TEAE for all indications with a statistically significantly higher frequency for duloxetine-treated patients compared with placebo-treated patients (all $p \leq 0.001$, except OAKP $p = 0.002$). In addition, the nausea rate was substantially lower for both the placebo- and duloxetine-treated groups in the CLBP and OAKP studies.

TEAEs by Population Demographics

Table IV provides information regarding TEAEs by patient subgroup for the most frequent adverse events. Duloxetine-treated patients experienced a higher overall rate of TEAEs regardless of age,

Table II. Patient demographics for the placebo-controlled studies

Characteristics	Placebo [n = 7496]	Duloxetine [n = 10 326]	p-Value[a]
Age [y; mean (SD)]	51.6 (13.7)	51.3 (13.6)	0.708
	Range 18–91	Range 18–91	
Race [n (%)][b]			0.043
Caucasian	5116 (83.6)	7510 (83.9)	
African	281 (4.6)	374 (4.2)	
Hispanic	383 (6.3)	607 (6.8)	
East Asian	272 (4.4)	305 (3.4)	
West Asian	12 (0.2)	48 (0.5)	
Native American	5 (0.1)	6 (0.1)	
other	47 (0.8)	97 (1.1)	
Sex [n (%)]			0.243
female	6225 (83.0)	8273 (80.1)	
male	1271 (17.0)	2053 (19.9)	

a Frequencies were analysed using the Cochran-Mantel-Haenszel test for general association controlling for study. Means were analysed using analysis of variance (ANOVA), and the model included the terms treatment and study.

b Some earlier studies did not capture the race of the participating patients. The number of patients with race data collected was placebo (n = 6116), duloxetine (n = 8947).

Table III. The percentage of most common treatment-emergent adverse events (TEAEs) overall and by indication[a]

TEAE (%)	Overall[b]	Indication						
		MDD[c]	DPNP[d]	GAD[e]	Fibromyalgia[f]	LUTD[g]	CLBP[h]	OAKP[i]
Any ≥1								
placebo	57.2	66.2	70.1	67.2	80.0	48.3	53.4	36.7
duloxetine	72.4***	74.4***	80.7***	77.6***	89.0***	67.2***	65.2*	50.2**
Nausea								
placebo	7.2	7.8	9.4	10.2	11.4	6.2	2.9	2.0
duloxetine	23.4***	21.0***	24.6***	33.8***	29.6***	22.8***	15.2***	8.4**
Dry mouth								
placebo	3.8	6.7	2.9	3.6	5.2	2.8	2.1	1.2
duloxetine	12.6***	15.0***	7.3**	11.6***	18.5***	12.1***	9.2***	3.3
Headache								
placebo	9.4	14.7	8.5	17.9	12.0	5.9	7.1	2.4
duloxetine	12.0***	14.4	11.1	16.3	20.1***	9.3***	6.7	2.9
Constipation								
placebo	3.1	4.4	3.8	3.5	3.6	2.7	0.8	0.8
duloxetine	10.1***	9.4***	9.5***	9.7***	14.4***	10.3***	8.0***	5.9**
Dizziness								
placebo	4.0	4.9	6.9	7.5	6.7	2.5	2.1	1.6
duloxetine	9.3***	8.7***	11.5**	13.5***	11.0*	8.6***	6.7*	4.2
Fatigue								
placebo	3.7	4.6	5.8	3.5	7.5	2.9	0.4	0.8
duloxetine	9.1***	7.9***	8.5	10.7***	13.7***	9.1***	6.2***	4.2*
Insomnia								
placebo	3.8	5.5	4.9	3.6	9.5	2.3	2.9	1.6
duloxetine	8.6***	8.3***	7.9	7.6**	14.8**	7.9***	10.0**	3.8
Diarrhoea								
placebo	4.8	7.3	6.5	5.6	8.0	3.1	4.2	2.4
duloxetine	7.5***	10.0***	9.6	7.9*	11.6*	4.9***	6.7	4.6
Somnolence								
placebo	1.6	2.5	5.1	1.8	2.8	0.7	0.4	1.6
duloxetine	6.9***	5.9***	15.9***	7.8***	9.7***	5.0***	6.7***	4.2
Hyperhidrosis								
placebo	1.3	2.0	1.8	2.0	1.1	0.9	0.4	0.4
duloxetine	5.6***	6.5***	8.5***	7.4***	6.8***	4.2***	3.2**	3.3*

a Common TEAEs were defined as those that occurred in ≥5% of the entire duloxetine group (n = 10 326); therefore, TEAEs in some indications will be <5%.

b No. of patients by indication: placebo n = 7496, duloxetine n = 10 326.

c No. of patients by indication: placebo n = 1625, duloxetine n = 2489.

d No. of patients by indication: placebo n = 448, duloxetine n = 906.

e No. of patients by indication: placebo n = 665, duloxetine n = 910.

f No. of patients by indication: placebo n = 535, duloxetine n = 876.

g No. of patients by indication: placebo n = 3737, duloxetine n = 4504.

h No. of patients by indication: placebo n = 238, duloxetine n = 402.

i No. of patients by indication: placebo n = 248, duloxetine n = 239.

CLBP = chronic lower back pain; **DPNP** = diabetic peripheral neuropathic pain; **GAD** = generalized anxiety disorder; **LUTD** = lower urinary tract disorders; **MDD** = major depressive disorder; **OAKP** = osteoarthritis knee pain; * $p \leq 0.05$ vs placebo, ** $p \leq 0.01$ vs placebo, *** $p \leq 0.001$ vs placebo.

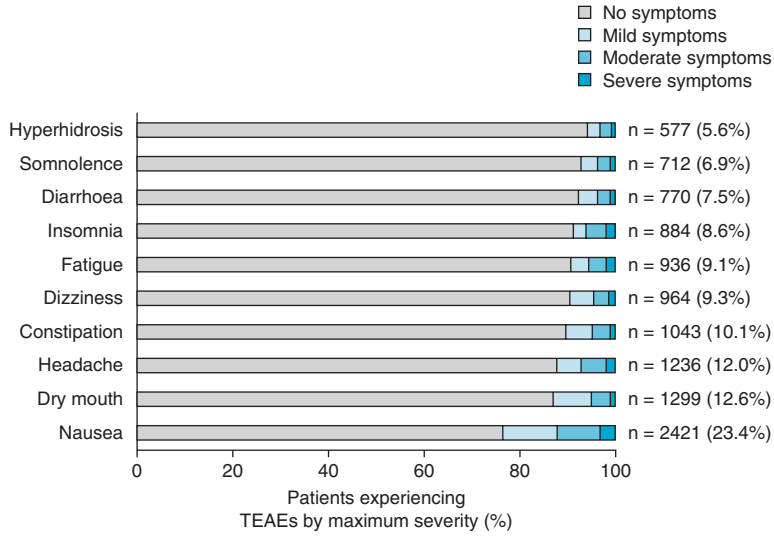

Fig. 1. Duloxetine treatment-emergent adverse events (TEAEs) by maximum severity. TEAEs reported by ≥5% of duloxetine-treated patients. Frequencies were analysed using the Cochran-Mantel-Haenszel test for general association controlling for study.

sex and race (all $p \leq 0.001$) compared with placebo-treated patients. All within-subgroup comparisons showed statistically significantly higher adverse event rates for duloxetine than placebo ($p \leq 0.05$) except for headaches in men (placebo 11.6%, duloxetine 12.2%, $p = 0.660$). No statistically significant treatment-by-subgroup interaction was found between age (<65 years and ≥65 years) and duloxetine treatment for any individual adverse event. In the analysis by sex, we observed a significant treatment-by-sex interaction for headache ($p = 0.068$), dry mouth ($p = 0.004$) and fatigue ($p = 0.030$). Men were more likely to experience headaches, whereas women were more likely to experience dry mouth and fatigue. Significant treatment-by-race interactions occurred for nausea ($p = 0.060$), dry mouth ($p = 0.040$), fatigue ($p = 0.072$) and diarrhoea ($p = 0.089$). Caucasian patients were more likely to experience these TEAEs than non-Caucasian patients, except for nausea.

TEAEs by Dose

We analysed the incidence of TEAEs by duloxetine dose administered (figure 2); for flexible dosing studies, the highest dose was used. Overall, we observed the highest frequency of TEAEs in the 90 mg/day duloxetine dosage subgroup (83.5%) and the lowest frequency in the 80 mg/day duloxetine dosage subgroup (66.9%). The duloxetine 120 mg/day dosage group had the highest incidence of constipation, fatigue, insomnia, somnolence and hyperhidrosis (12.5%, 10.5%, 10.6%, 10.4% and 8.3%, respectively). Dry mouth (14.8%) was most commonly reported in the duloxetine 60 mg/day group whereas nausea (32.2%), headache (17.4%), dizziness (17.4%) and diarrhoea (11.3%) had the highest incidence in the duloxetine 90 mg/day dosage group. Eight of the ten most common TEAEs occurred at the lowest rate in the 40 mg/day or <40 mg/day dosage groups.

Onset and Duration of TEAEs

The first onset of the five most common TEAEs is shown in figure 3, whereas the median duration of the five most common TEAEs is presented in table V. The first onset for each of the most common TEAEs occurred primarily in the first week of treatment (the spikes may be related to the scheduled visit intervals in individual studies). Although not shown, TEAEs in the placebo group also tended to have their first onset in the first week of treatment. The rate of duloxetine-associated nausea was highest in the

Table IV. Treatment-emergent adverse events (TEAEs) frequency by patient demographics[a]

TEAE (%)	Sex[b]				Race[c]				Age[d]			
	female		male		Caucasian		other		<65 y		≥65 y	
	placebo (n = 6225)	DLX (n = 8273)	placebo (n = 1271)	DLX (n = 2053)	placebo (n = 5116)	DLX (n = 7510)	placebo (n = 2380)	DLX (n = 2816)	placebo (n = 6170)	DLX (n = 8523)	placebo (n = 1326)	DLX (n = 1803)
≥1 TEAE[e]	56.5	71.8	60.6	75.0	61.4	74.5	48.2	66.9	58.2	73.6	52.3	67.0
Nausea[f]	7.6	24.5	5.2	19.2	6.6	22.8	8.6	25.1	7.5	24.3	5.9	19.6
Headache[g]	8.9	11.9	11.6	12.2	10.0	12.2	8.0	11.4	10.3	12.8	5.1	8.2
Dry mouth[f,g]	3.7	13.1	4.7	10.4	3.8	13.2	3.9	11.0	4.0	12.4	3.3	13.3
Constipation	3.3	10.7	2.2	7.7	3.1	10.1	3.2	10.2	3.1	9.5	3.4	12.9
Dizziness	3.9	9.0	4.6	10.7	4.1	9.1	3.7	9.9	3.9	9.4	4.3	9.2
Fatigue[f,g]	3.6	9.4	4.2	7.6	4.4	9.7	2.2	7.3	3.8	9.3	3.3	7.9
Insomnia	3.7	8.8	4.0	7.5	4.2	9.1	2.9	7.1	4.1	9.2	2.3	5.5
Diarrhoea[f]	4.6	7.0	5.5	9.3	5.1	8.2	3.9	5.4	5.0	7.7	3.5	6.4
Somnolence	1.5	6.6	2.3	8.0	1.7	7.0	1.6	6.7	1.7	6.9	1.6	6.9
Hyperhidrosis	1.2	5.3	1.5	6.6	1.3	6.0	1.3	4.5	1.3	5.5	1.2	6.0

a TEAEs with a significantly greater frequency in the duloxetine-treated group vs placebo and frequency ≥5% are presented. Fisher's exact test and Chi-squared test were used to calculate p-values for all within-strata comparisons of duloxetine with placebo.

b All within-strata comparisons of duloxetine with placebo were $p < 0.001$ except for 'male' in headache ($p = 0.660$).

c All within-strata comparisons of duloxetine with placebo were $p < 0.001$ except for 'other' in diarrhoea ($p = 0.013$).

d All within-strata comparisons of duloxetine with placebo were $p < 0.001$.

e In age comparisons, the only significant treatment-by-subgroup interaction was for overall TEAEs (0.049).

f In race comparisons, significant treatment-by-subgroup interaction occurred for nausea (0.060), dry mouth (0.040), fatigue (0.072) and diarrhoea (0.089).

g In sex comparisons, significant treatment-by-subgroup interactions occurred for headache (0.068), dry mouth (0.004) and fatigue (0.030).

DLX = duloxetine.

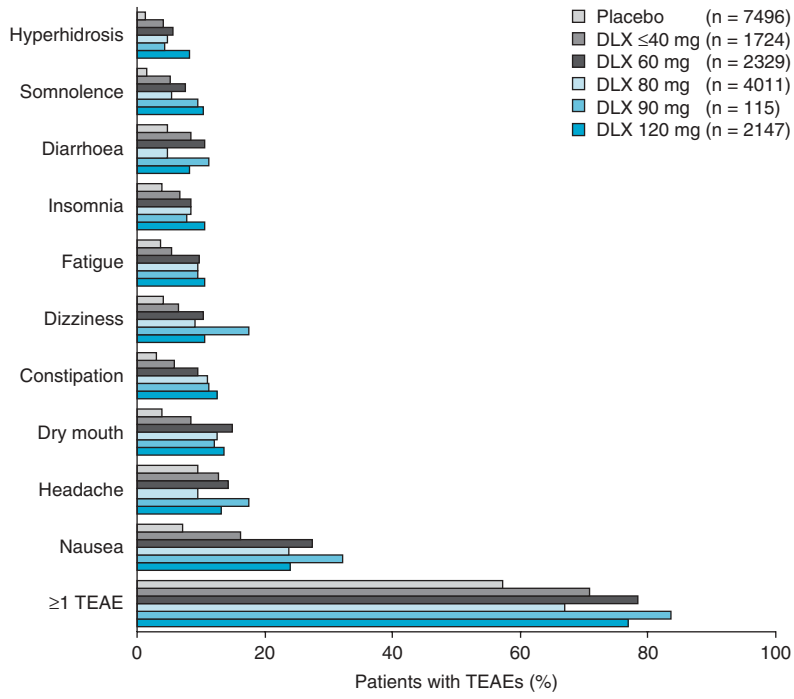

Fig. 2. Treatment-emergent adverse events (TEAEs) by duloxetine (DLX) dose. Only TEAEs with incidence ≥5% in the DLX group are shown. For flexible dosing studies, the highest dose was used in the analysis. The Cochran-Mantel-Haenszel test was used to determine the general association between TEAE and dose ($p \leq 0.001$ for each event).

first week of treatment (19.6%) with a median duration of 8 days.

Discontinuations due to Adverse Events (DCAEs)

The overall rate of discontinuations due to adverse events (DCAEs) was 14.0% in duloxetine-treated patients and 4.6% in placebo-treated patients ($p \leq 0.001$). Nausea (3.0%) was the most common reason for DCAE in duloxetine-treated patients followed by dizziness (0.8%), fatigue (0.8%), insomnia (0.7%) and somnolence (0.7%) (figure 4). Rates for these five DCAEs in the placebo group were 0.5%, 0.3%, 0.1%, 0.2% and 0.0%, respectively. All duloxetine versus placebo comparisons were significant at the $p \leq 0.01$ level.

DCAEs by Dose

There was no clear dose response, although the dosage with the greatest discontinuation rate was 80 mg/day or higher for each of the DCAEs, with the exception of diarrhoea. For diarrhoea, the highest discontinuation rate was in the

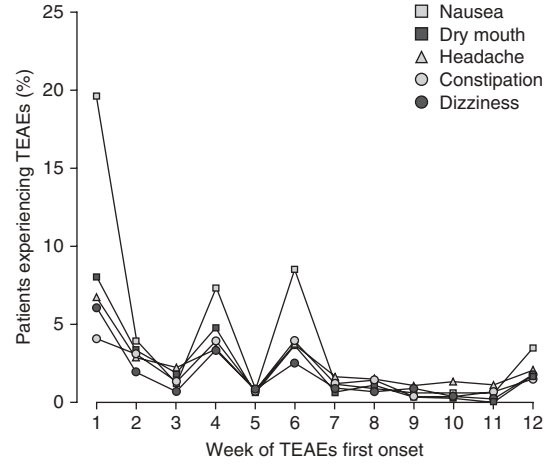

Fig. 3. Time to onset of treatment-emergent adverse events (TEAEs) in weeks. The five most common TEAEs are included.

Table V. Median time of duration of treatment-emergent adverse events (TEAEs)

TEAE	Duration (days)	
	placebo	duloxetine
Nausea	10	8
Headache	16	9
Dry mouth	38	73
Constipation	33	46
Dizziness	16	8
Fatigue	65	39
Insomnia	53	41
Diarrhoea	5	4
Somnolence	42	31
Hyperhidrosis	28	63

≤40 mg/day dosage group (figure 5). The 60 mg/day dosage did not have the highest discontinuation rate for any of the most common DCAEs. The lowest discontinuation rates were most commonly in the ≤40 mg/day dosage group.

Discussion

Our results show that there is a higher rate of TEAEs in duloxetine-treated patients when compared with patients receiving placebo; however, the TEAEs observed were mainly mild to moderate in severity and of a short duration. Nausea was the most common TEAE experienced by patients for all indications and for each dose of duloxetine, with a mild-to-moderate intensity. We also found that the onset of the most common TEAEs occurred early in the treatment period; for example, nausea occurred in 20% of patients during the first week of treatment, then considerably decreased to the second week of treatment, with a rate of <5%. The mean duration of nausea was 8 days. A total of 2376 (23.4%) patients treated with duloxetine experienced nausea at some point during treatment.

In the pooled duloxetine clinical trials, 14% of duloxetine-treated patients discontinued treatment early due to adverse events. This rate is similar to what has been found with the SNRI venlafaxine in a pooled analysis[57] and in a study of patients with GAD that included both duloxetine and venlafaxine.[38] However, we believe that treatment adherence could be improved if physicians better understood the characteristics of the TEAEs that may present when using duloxetine for the treatment of the various conditions. Clinicians could explain to their patients the transient nature of many of the TEAEs noted with duloxetine. In addition, nausea, which was the most common reason for discontinuation in this study (3%), has been found to be less of a problem when duloxetine is taken with food or initiated at a lower dose and escalated gradually.[58,59] Importantly, healthcare providers should clarify with their patients which adverse events are not serious and encourage them not to discontinue their medication without first talking with their doctor.

The most striking observation from the analysis of the proportions of patients experiencing TEAEs by indication was the much lower TEAE rates in the OAKP studies (HMEP;[20] HMFG, unpublished). We believe there are several potential reasons for this result. First, these are the most recent studies and the knowledge obtained from the previous studies may have contributed to this finding. For instance, in the OAKP studies, randomly assigned patients received duloxetine 30 mg/day for 1 week before titrating to 60 mg/day. This tends to lower the percentage of patients experiencing nausea and perhaps some other TEAEs.[58,59] Moreover, in the OAKP studies, patients were instructed to take the study drug with a meal, which also reduces the probability of

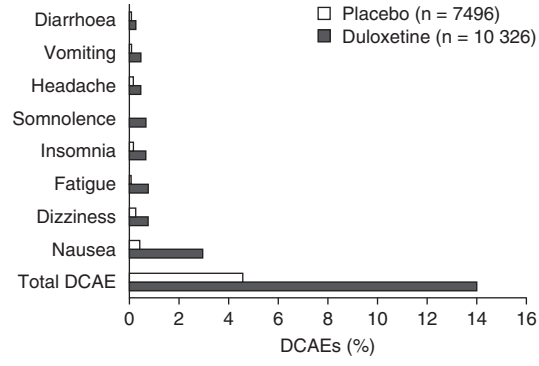

Fig. 4. Discontinuations due to adverse events (DCAEs). Only the adverse events most frequently leading to discontinuation are shown. All duloxetine vs placebo comparisons were significant at the $p \leq 0.01$ level (calculated using Cochran-Mantel-Haenszel test for general association controlling for study).

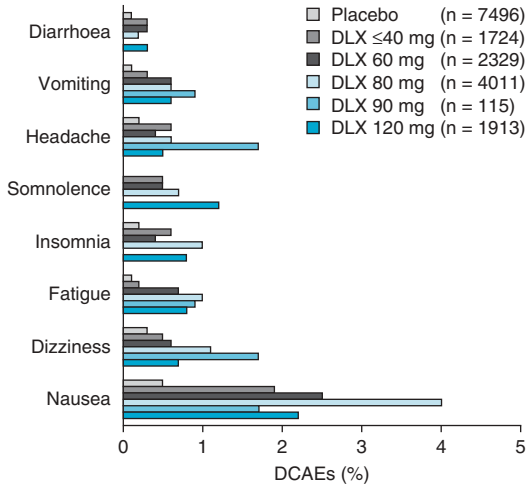

Fig. 5. Discontinuations due to adverse events (DCAEs) by duloxetine (DLX) dose. Only the adverse events most frequently leading to discontinuation are listed. For flexible dosing studies, the highest dose was used in the analysis. The Cochran-Mantel-Haenszel test was used to determine the general association between TEAE and dose ($p \leq 0.01$).

experiencing nausea.[58,59] In many of the earlier studies, especially in MDD, patients were instructed to take the study drug without regard to meals. In addition, patients in the OAKP studies were allowed to take NSAIDS, which may lower the incidence of certain TEAEs.

In contrast, fibromyalgia was the indication associated with the highest proportion of patients experiencing TEAEs in both the placebo and duloxetine treatment groups, even though these patients were allowed paracetamol (acetaminophen) [up to 2 g/day] and aspirin (acetylsalicylic acid) [up to 325 mg/day]. However, patients with fibromyalgia are known to have a high rate of comorbidities and associated symptoms, which may explain this high incidence of TEAEs.[60]

Statistically significant differences in the frequency of TEAEs were observed between placebo and duloxetine recipients when stratified by sex, age and race. The exception was headaches in males, which was not surprising because the rates of this adverse event do not usually show statistically significant differences between duloxetine and placebo treatment groups in individual studies.[15,24,39,52] No significant treatment-by-subgroup differences were found in the overall TEAE frequency by sex or race. Interestingly, for those taking duloxetine, a lower percentage of older patients (aged ≥65 years) experienced TEAEs than younger patients (nearly 7% lower). However, there were no significant treatment-by-subgroup interactions for any of the individual TEAEs within the age subgroup. These results suggest that a higher incidence of TEAEs would not be expected for older patients taking duloxetine compared with younger patients. Indeed, in a previous analysis of older patients (comparison of patients aged ≥75 with those aged <75 years), the older subgroup also had a slightly lower rate of TEAEs.[61]

There were significant sex-by-treatment interactions for headache, dry mouth and fatigue, with dry mouth and fatigue more likely to occur in women. At least part of the reason for these significant interactions between treatment and sex could be that 95% of patients with fibromyalgia were women, and patients with fibromyalgia were shown to have the highest TEAE rates of any indication. In contrast, a pooled analysis of seven trials in patients with MDD found no significant differences in TEAE rates between men and women, except for higher rates of nausea in women; however, the significance was driven by nausea rates that were 3-fold higher in women taking placebo compared with men taking placebo.[62] We also found four significant race-by-treatment interactions (nausea, dry mouth, fatigue and diarrhoea), with each, except nausea, being more likely to occur in Caucasian patients than non-Caucasian patients. A study of duloxetine in patients with MDD found no significant differences in adverse event profiles between Caucasian and Hispanic patients.[63] However, a study of duloxetine for SUI found significant differences in the rates of adverse events in African American (dry mouth, insomnia and constipation; all lower) and Hispanic (fatigue, constipation, dizziness, headache and somnolence; fatigue and constipation lower, the other three higher) patients compared with Caucasian patients.[64] Therefore, it is not surprising there were some differences in TEAE rates between Caucasian and non-Caucasian patients.

Although there was a clear trend in rates of TEAEs by dosage from placebo to duloxetine

40 mg/day and from duloxetine 40 mg/day to 60 mg/day, there was not an obvious trend for dosages above 60 mg/day. We also noted that the 80 mg/day dosage group mostly had lower TEAE rates than the 60 mg/day group. This likely occurred because most patients taking 80 mg/day came from the LUTD population. Overall, these patients tend to be healthier than those from other populations. We also observed that the rate of TEAEs for the 120 mg/day dosage group did not significantly differ from those for the other dosage groups. This can be explained primarily by the fact that most patients in the 120 mg/day dosage group had dosage escalations from 60 to 120 mg/day. As we have shown, most TEAEs occur early in treatment; therefore, it is not surprising that we did not observe significant differences in rates of TEAEs between the 60 and 120 mg/day groups.

Our findings are consistent with previously published papers on the safety and tolerability of duloxetine treatment. This pooled analysis contributes to a greater understanding of the adverse event profile of duloxetine treatment. Previous pooled analyses, including a study analysing the safety profile of 23 983 patients treated with duloxetine,[16] have given insight into the safety profile of duloxetine; however, that study included patients from both placebo-controlled and open-label studies. Nevertheless, the adverse event profiles from that study are very similar to those in the present analysis, which only included placebo-controlled trials. The most common adverse events in the previous pooled analysis[16] were nausea, headache, dry mouth, insomnia, constipation, dizziness, fatigue, somnolence, diarrhoea and hyperhidrosis. This previous study also reported that nausea was the most common adverse event, had a mild to moderate severity, appeared early in the course of treatment and became less prevalent over subsequent weeks. These data are consistent with the findings of our present analysis.

This is the first analysis on the tolerability of duloxetine conducted using only randomized, double-blind, placebo-controlled trials to report a statistical comparison between subgroups; this was not previously analysed in other pooled analyses. We addressed questions regarding differences in TEAE severity, onset and resolution of these events in a large pooled database. We found that TEAEs were significantly more frequent in duloxetine-treated patients regardless of patient demographics or treatment indications. A 2007 study[16] reported that the adverse events were consistent with the known pharmacology of duloxetine, rather than attributable to a specific condition, with the limitation that no statistical comparison was made between duloxetine and placebo in that analysis. Our results show that placebo- and duloxetine-treated patients have similar types of adverse events with each treatment indication and that individual variations in frequency could be attributable to the underlying pathology rather than to a particular effect of duloxetine in any given treatment indication.

Conclusions

For duloxetine, most adverse events tend to be mild and transitory in nature. Although there was no clear relationship between treatment dosage and TEAE, the general tendency was a lower rate of TEAEs and DCAEs in duloxetine dosages ≤60 mg/day. The types of adverse events are consistent across treatment indications, and by different demographic variables such as age, sex and race.

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