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Brief report

Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder ☆

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Abstract

Background: Discontinuation symptoms are common following antidepressant treatment. This report characterizes symptoms following duloxetine discontinuation.
Methods: Data were obtained from 9 clinical trials assessing the efficacy and safety of duloxetine in the treatment of major depressive disorder (MDD).
Results: In a pooled analysis of 6 short-term treatment trials, in which treatment was stopped abruptly, discontinuation-emergent adverse events (DEAEs) were reported by 44.3% and 22.9% of duloxetine- and placebo-treated patients, respectively ($p<0.05$). Among duloxetine-treated patients reporting at least 1 DEAE, the mean number of symptoms was 2.4. DEAEs reported significantly more frequently on abrupt discontinuation of duloxetine compared with placebo were dizziness (12.4%), nausea (5.9%), headache (5.3%), paresthesia (2.9%), vomiting (2.4%), irritability (2.4%), and nightmares (2.0%). Dizziness was also the most frequently reported DEAE in the analyses of 3 long-term duloxetine studies. Across the short- and long-term data sets, 45.1% of DEAEs had resolved in the duloxetine-treated populations by the end of the respective studies, and the majority of these (65.0%) resolved within 7 days. Most patients rated the severity of their symptoms as mild or moderate. A higher proportion of patients reporting DEAEs were seen with 120 mg/day duloxetine compared with lower doses. For doses between 40 and 120 mg/day duloxetine the proportion of patients reporting at least one DEAE differed significantly from placebo. Extended treatment with duloxetine beyond 8–9 weeks did not appear to be associated with an increased incidence or severity of DEAEs.
Conclusions: Abrupt discontinuation of duloxetine is associated with a DEAE profile similar to that seen with other selective serotonin reuptake inhibitor (SSRI) and selective serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressants. It is

☆ Declaration of interest. David Perahia, Daniel Kajdasz, and Durisala Desaiah are employees of Eli Lilly and Company. Peter Haddad has received payment from Eli Lilly and Company and other pharmaceutical companies for attending advisory boards, lecturing and consultancy work.

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recommended that, whenever possible, clinicians gradually reduce the dose no less than 2 weeks before discontinuation of duloxetine treatment.
Limitations: The main limitation is the use of spontaneously reported DEAEs.

Keywords: Duloxetine; Discontinuation; Antidepressant; Safety/tolerability; Adverse events

1. Introduction

Discontinuation-emergent adverse events (DEAEs) have been documented with tricyclic antidepressants (Ceccherini-Nelli et al., 1993; Dilsaver and Greden, 1984), monoamine oxidase inhibitors (Halle and Dilsaver, 1993), SSRIs (Rosenbaum and Zajecka, 1997) and more recently launched antidepressants including venlafaxine, mirtazapine, and nefazodone (Benazzi, 1998; Fava et al., 1997; MacCall and Callender, 1999). Symptoms usually commence within a few days of stopping an antidepressant, are mild and short-lived, and resolve within 1 week without treatment (Haddad, 2001). In a minority of patients, however, symptoms can be severe and last many weeks (Haddad et al., 2001). Symptoms may be misdiagnosed, for example as a relapse or recurrence of depression. This report aims to characterize DEAEs associated with duloxetine hydrochloride (Cymbalta®), a new SNRI recently approved in several countries for the treatment of MDD.

2. Methods

Data were reviewed from 9 multi-center clinical trials conducted in the United States (studies 1–6), Europe (studies 7 and 8), and Latin America (study 9) examining the efficacy and safety of duloxetine in MDD (Table 1). All studies were funded, designed and conducted by Eli Lilly and Company (Detke et al., 2003a; Detke et al., 2003b; Nemeroff et al., 2002; Raskin et al., 2003). Eight studies were randomized, double blind, placebo-controlled trials that examined 8–9 weeks of acute treatment, of which 2 had a 26-week placebo-controlled extension phase (studies 7 and 8). Study 9 was a 52-week open-label trial.

Study patients were depressed as defined by the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) and confirmed by the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1981); they had a total score ≥ 15 on the $HAMD_{17}$ and ≥ 4 on the Clinical Global Impression-Severity (CGI-S) scale at baseline. The inclusion and exclusion criteria of the patients in all 9 trials have been previously published (Nemeroff et al., 2002; Greist et al., 2004).

In all studies, duloxetine was abruptly discontinued, followed by a lead-out phase of 1 or 2 weeks to allow for the collection of DEAEs at a set time after the discontinuation of duloxetine or placebo. In the placebo-controlled studies, patients received placebo during the lead-out phase; investigators and patients were blinded to the exact study visit at which the placebo lead-out phase would commence. DEAEs were elicited by non-probing inquiry, recorded regardless of perceived causality, and rated as mild, moderate, or severe. Events were registered as DEAEs if they occurred for the first time or worsened following discontinuation of treatment with reference to the treatment-emergent adverse events occurring during the prior treatment period. The incidence rates presented are based on those patients who entered the lead-out phase for each study. The duration of DEAEs resolved at the end of each study was determined as a function of time in days.

3. Results

3.1. Acute treatment (studies 1 to 6, Table 1)

Significantly more duloxetine-treated patients (44.3%) reported at least 1 DEAE than placebo-treated patients (22.9%), with dizziness being the most common symptom (Table 2). Two hundred and seventeen duloxetine-treated patients reported at least 1 DEAE, with a total of 510 separate events being reported. Of the 510 events reported, 203 (39.8%) were mild, 258 (50.6%) were moderate and 49 (9.6%)

Table 1
Summary of clinical trials

Study	Study design	Treatments (*N*)	Weeks of treatment
1	Parallel, double-blind, placebo-controlled, randomized, fluoxetine-controlled	Placebo (70) Duloxetine 20–60 mg BID[a] (70) Fluoxetine 20 mg QD (33) Total (173)	8
2	Parallel, double-blind, placebo-controlled, randomized, fluoxetine-controlled	Placebo (75) Duloxetine 20–60 mg BID[a] (82) Fluoxetine 20 mg QD (37) Total (194)	8
3	Parallel, double-blind, placebo-controlled, randomized	Placebo (122) Duloxetine 60 mg QD (123) Total (245)	9
4	Parallel, double-blind, placebo-controlled, randomized	Placebo (139) Duloxetine 60 mg QD (128) Total (267)	9
5	Parallel, double-blind, placebo-controlled, randomized, paroxetine-controlled	Placebo (90) Duloxetine 20 mg BID (91) Duloxetine 40 mg BID (84) Paroxetine 20 mg QD (89) Total (354)	8
6	Parallel, double-blind, placebo-controlled, randomized, paroxetine-controlled	Placebo (89) Duloxetine 20 mg BID (86) Duloxetine 40 mg BID (91) Paroxetine 20 mg QD (87) Total (353)	8
7	Parallel, double-blind, placebo-controlled, randomized, paroxetine-controlled	Placebo (93) Duloxetine 40 mg BID (93) Duloxetine 60 mg BID (95) Paroxetine 20 mg QD (86) Total (367)	8; +26-week extension phase
8	Parallel, double-blind, placebo-controlled, randomized, paroxetine-controlled	Placebo (99) Duloxetine 40 mg BID (93) Duloxetine 60 mg BID (103) Paroxetine 20 mg QD (97) Total (392)	8; +26-week extension phase
9	Open-label	Duloxetine 40–60 mg BID (1279)	52

In all these studies, the observation period for DEAEs is 2 weeks; BID=twice daily; QD=once daily.
[a] Forced titration to 120 mg/day.

were severe. Eighty-seven placebo-treated patients reported at least 1 DEAE, with a total of 139 separate events being reported. Of the 139 events, 64 (46.0%) were mild, 68 (48.9%) were moderate, and 7 (5.0%) were severe. A total of 15 (3.1%) duloxetine-treated patients and no placebo-treated patients withdrew from these studies due to a DEAE. Four patients reported dizziness as the reason for study discontinuation.

DEAEs were analyzed according to the dose taken immediately prior to discontinuation of acute treatment. DEAEs were reported by 22.9%, 42.4%, 39.2%, 36.9%, and 62.1% of patients receiving placebo, duloxetine 40, 60, 80, and 120 mg/day, respectively. A higher incidence of DEAEs was seen with 120 mg/day duloxetine compared with lower doses, but the relationship between dose and the proportion of patients reporting DEAEs is not linear as similar incidences were reported for patients taking 40, 60 or 80 mg/day of duloxetine. Furthermore, patients treated with 40, 60 80 and 120 mg/day of duloxetine reported significantly more DEAEs than patients treated with placebo ($p<0.01$).

In terms of the duration of DEAEs reported by patients following duloxetine discontinuation, 46.3% had resolved prior to final contact with study patients, and the remaining 53.7% were unresolved. Of the

Table 2
Discontinuation-emergent adverse events after acute treatment reported by at least 2% of duloxetine-treated patients who entered the lead-out phase of studies 1, 2, 3, 4, 5 and 6

Event	Placebo (N=380; n (%))	Duloxetine (N=490; n (%))
Patients with ≥ 1 event	87 (22.9)	217 (44.3)*
Dizziness	3 (0.8)	61 (12.4)*
Nausea	1 (0.3)	29 (5.9)*
Headache NOS	3 (0.8)	26 (5.3)*
Paraesthesia	1 (0.3)	14 (2.9)*
Diarrhea NOS	3 (0.8)	11 (2.2)
Vomiting NOS	2 (0.5)	12 (2.4)*
Irritability	1 (0.3)	12 (2.4)*
Insomnia	2 (0.5)	10 (2.0)
Nightmare	0 (0.0)	10 (2.0)*

NOS=not otherwise specified.
* P<0.05 vs. placebo, Fisher's Exact Test.

resolved DEAEs, 30.5% had resolved within 1–2 days of duloxetine discontinuation, 37.7% within 3–7 days, and 31.8% resolved after 7 days but prior to final study contact. In patients previously receiving placebo, 47.5% of DEAEs had resolved prior to final study contact and 52.5% were unresolved. Of the resolved DEAEs, 47.0% had resolved within 1–2 days, 37.9% within 3–7 days, and 15.1% after 7 days but prior to final study contact.

3.2. Placebo-controlled long-term treatment (studies 7 and 8, Table 1)

Significantly more duloxetine-treated patients reported at least 1 DEAE (9.1%) than did placebo-treated patients (2.0%) with dizziness being the most common symptom (Table 3). Twenty-two patients reported at least 1 DEAE, with a total of 34 DEAEs being reported. Of the 34 DEAEs reported, 24 (70.6%) were mild, 9 (26.5%) were moderate, and 1 (2.9%) was severe. One patient treated with duloxetine discontinued due to dizziness during the lead-out phase. In terms of the duration of DEAEs reported by patients following duloxetine discontinuation, 35.3% of DEAEs had resolved prior to final contact with study patients and the remaining 64.7% were unresolved. Of the resolved DEAEs, 16.7% had resolved within 1–2 days of duloxetine discontinuation, 25.0% within 3–7 days, and 58.3% after 7 days but prior to final study contact. In patients receiving placebo, 1 out of the 2 reported DEAEs resolved within 7 days. Contrary to the findings associated with short-term exposure, no difference was seen in the number of patients reporting at least 1 DEAE between the 80 and 120 mg/day groups after abrupt discontinuation after long-term treatment with duloxetine.

3.3. Open-label 52-week treatment (study 9, Table 1)

In the uncontrolled 52-week open label study, half of the patients reported at least 1 DEAE with dizziness being the most common symptom (Table 4). Among the 281 patients reporting at least 1 DEAE, there were a total of 793 DEAEs reported of which 290 (36.6%) were reported as being of mild severity, 367 (46.3%) moderate, and 136 (17.2%) severe. Prior to final contact with study patients 44.8% DEAEs had resolved and the remaining 55.2% were unresolved. Of the resolved DEAEs, 9.1% had resolved within 1–2 days of duloxetine discontinuation, 54.6% within 3–

Table 3
Discontinuation-emergent adverse events after long-term treatment occurring in at least 2 duloxetine-treated patients by dose

Event	Placebo (N=101; n (%))	DLX 80 mg/day (40 mg/BID) (N=118; n (%))	DLX 120 mg/day (60 mg BID) (N=124; n (%))	DLX total (N=242; n (%))
Patient with>1 DEAE	2 (2.0)	10 (8.5)*	12 (9.7)*	22 (9.1)*
Dizziness	1 (1.0)	4 (3.4)	4 (3.2)	8 (3.3)
Anxiety	0 (0.0)	1 (0.8)	1 (0.8)	2 (0.8)
Headache NOS	0 (0.0)	0 (0.0)	2 (1.6)	2 (0.8)
Irritability	0 (0.0)	1 (0.8)	1 (0.8)	2 (0.8)
Nausea	0 (0.0)	0 (0.0)	2 (1.6)	2 (0.8)
Vomiting NOS	0 (0.0)	0 (0.0)	2 (1.6)	2 (0.8)

Data are from patients who entered the lead-out phase of studies 7 and 8.
DLX=duloxetine; NOS=not otherwise specified; BID=twice daily.
* P<0.05 vs. placebo, Fisher's Exact Test.

Table 4
Discontinuation-emergent adverse events after long-term treatment for which the incidence was at least 2%

Event	Duloxetine ($N=553$; n (%))
Patients with ≥ 1 DEAE	281 (50.8)
Dizziness (excluding vertigo)	106 (19.2)
Anxiety NEC	55 (9.9)
Nausea	54 (9.8)
Headache NOS	40 (7.2)
Insomnia	37 (6.7)
Irritability	33 (6.0)
Vomiting NOS	24 (4.3)
Nightmare	16 (2.9)
Paraesthesia	16 (2.9)
Tinnitus	16 (2.9)
Crying	15 (2.7)
Depressed mood	15 (2.7)
Depression NOS	15 (2.7)
Anorexia	14 (2.5)
Diarrhea NOS	14 (2.5)
Myalgia	13 (2.4)
Tremor	12 (2.2)
Nervousness	11 (2.0)

NEC = not elsewhere classified; NOS = not otherwise specified.

7 days, and 36.3% after 7 days but prior to final study contact.

4. Discussion

The pattern of DEAEs seen across all 3 groups of studies (short-term placebo-controlled, long-term placebo-controlled, and the long-term open-label study) was similar (Tables 2–4). In all 3 groups, dizziness was the most common DEAE in duloxetine-treated patients, with nausea and headache also consistently reported. This symptom profile is similar to that reported with SSRIs and venlafaxine (Haddad, 2001). A majority of patients who experienced DEAEs described them as mild to moderate in severity. Consistent with this and across all 9 studies, only 22 (1.7%) patients out of the total of 1285 who entered the lead-out phases discontinued study participation due to DEAEs.

When the pooled incidence rate for DEAEs in the 6 short-term studies was compared with that seen in the 3 long-term studies, a slightly higher rate was observed in the 52-week open-label study. This may be explained in part by the absence of blinding in the long-term open-label study and the fact that patients therefore knew for certain when active drug was being discontinued (unique to this study). The proportions of DEAEs rated as severe by duloxetine-treated patients were similar in both short-term and long-term placebo-controlled studies. Overall, the comparisons suggest that the incidence and severity of DEAEs is not increased significantly when the duration of duloxetine treatment is extended beyond 8 or 9 weeks. This finding is consistent with data reported for other antidepressants (Baldwin et al., 2005).

Overall, 45.1% of DEAEs had resolved prior to final contact with study patients receiving duloxetine, and of these resolved DEAEs, 68.2%, 47.1%, and 63.7% had resolved within 7 days of duloxetine discontinuation in studies 1–6, 7 and 8, and 9, respectively. It is of note that the proportion of DEAEs resolved at the final study contact was similar for duloxetine and placebo regardless of duration of treatment.

Given that the majority of duloxetine DEAEs were rated as mild to moderate in severity, reassurance by the clinician may be all that is required for most patients (Haddad, 2001; Rosenbaum and Zajecka, 1997). For more severe symptoms the prescribing clinician may wish to consider reinstating the original dose and slowing the rate of taper. Consistent with this, the current European Union Summary of Product Characteristics for duloxetine recommends a gradual reduction in the dose over no less than 2 weeks before discontinuation, while the U.S. Product Information for duloxetine recommends a gradual reduction of the dose whenever possible. The main limitation of this review is that DEAEs were assessed by means of spontaneous reports rather than a symptom checklist. The latter might be expected to produce higher incidence rates. The occurrence of DEAEs in the placebo arms emphasizes the importance of using placebo-controlled studies to assess DEAEs.

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