Duloxetine Treatment of Stress Urinary Incontinence in Women Does Not Induce Mania or Hypomania

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Background: Mania is a rare but unwelcome side effect of treating depressed patients with antidepressants. This research sought to determine the risk of treatment-emergent mania or hypomania in women with stress urinary incontinence treated with duloxetine, a balanced dual serotonin-norepinephrine reuptake inhibitor currently under investigation for the treatment of both stress urinary incontinence and major depressive disorder.

Method: Data were obtained from 4 double-blind, randomized, placebo-controlled studies involving 1913 women aged 22 to 83 years and 4 ongoing uncontrolled longer-term studies involving 1877 women aged 20 to 87 years. In all studies, women had the predominant symptom of stress urinary incontinence; in the active treatment arms, all women received duloxetine 80 mg/day. Women receiving antidepressants for major depressive disorder were excluded. In the placebo-controlled studies, 1 woman reported a history of bipolar disorder and 74 women reported a history of depression. In the uncontrolled longer-term studies, 1 woman reported a history of bipolar disorder and 69 reported a history of depression.

Results: In the placebo-controlled trials, 1 woman treated with duloxetine reported euphoria, while 1 reported mania and 1 reported euphoria when on placebo. In the uncontrolled longer-term studies, 1 woman reported mania; 1, euphoria; and 4, elevated moods. No women discontinued the study due to treatment-emergent mood elevation.

Conclusion: These data suggest that duloxetine does not induce mania or hypomania in women with stress urinary incontinence in this population, in which few women had a history of bipolar disorder or depression and women on antidepressants were excluded.

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Duloxetine hydrochloride [LY248686, (+)-(S)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride] belongs to a new generation of antidepressants. It is a potent and relatively balanced dual reuptake inhibitor of both serotonin and norepinephrine (SNRI)[1] that is currently being investigated for the treatment of major depressive disorder (MDD)[2] and female stress urinary incontinence (SUI).[3] SUI is the complaint of involuntary leakage of urine associated with effort, exertion, sneezing, or coughing.[4]

The prevalence of urinary incontinence (UI), defined as any involuntary leakage of urine,[4] has been estimated in all women at 28%,[5] with 78% of women presenting with symptoms of SUI in either pure (49%) or mixed (29%) forms.[6] The prevalence of SUI increases gradually and peaks in the fourth to sixth decades of life.[5] Although a variety of off-label agents are often prescribed, no medication has been approved worldwide for the treatment of SUI before now. As of August 13, 2004, duloxetine 40 mg twice daily has been granted marketing authorization across the European Union for the treatment of moderate to severe SUI in women. In animal studies, duloxetine has been demonstrated to increase bladder capacity and striated urethral sphincter muscle activity during the storage phase of the micturition cycle, presumably via elevated levels of serotonin and norepinephrine in the sacral spinal cord.[7] A similar central mechanism is believed to explain the reduced incontinence episode frequency (IEF) experienced in women with SUI. The IEF is the subject's count of the number of incontinent episodes recorded in real time on paper diaries during a 7-day period. This measure-

ment is well established within incontinence research, and IEF was the primary efficacy measure in all 4 trials presented in this article.

The clinical efficacy of duloxetine as a treatment for SUI was established in 4 randomized, double-blind, placebo-controlled 12-week studies involving 1913 adult women, aged 22 to 83 years, meeting validated clinical criteria for SUI.[3] In each of the 4 studies, the duloxetine-treated patient group had a 50% or greater median decrease in IEF, significantly better than the placebo-treated group's response. These significant and clinically relevant improvements in IEF were mirrored by significant improvements in condition-specific measures of quality of life.

The mechanism of the antidepressant action of duloxetine in humans is believed to be related to potentiation of serotonergic and norepinephrinergic activity in the central nervous system. The clinical efficacy of duloxetine as a treatment for unipolar MDD has been demonstrated in 4 randomized, double-blind, placebo-controlled studies[3,19,20,21] involving over 1000 men and women meeting DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition) criteria for MDD. In these 4 studies, duloxetine demonstrated superiority over placebo as measured by improvement in the 17-item Hamilton Rating Scale for Depression (HAM-D-17) total score.

While the risk of antidepressant-induced mania or hypomania in the patient with no previous history of mood disorders has not been systematically investigated, mania and hypomania are well known to occur in a small but significant proportion of depressed patients undergoing treatment with an antidepressant. Such treatment-induced elevation of mood may occur even in patients without the bipolar form of depression in which mood elevations are characteristic of the illness. In patients with unipolar depression, manic switch on antidepressant treatment has been reported in less than 1% of patients, while manic switch in depressed individuals with bipolar disorder is considerably higher at between 3.7% and 11.2%, with the risk depending on the type of antidepressant taken.[8] While the older tricyclic antidepressants have been reported to carry the greatest risk,[8] the risk associated with SNRIs is currently unknown.

The safety of duloxetine has been established in both SUI and MDD studies; however, a comprehensive analysis of elevated-mood effects in women with SUI has not been presented before. The objective of this article is to review the risk of treatment-emergent mania or hypomania in women treated with duloxetine for SUI.

METHOD

Data were obtained from 1913 women aged 22 to 83 years enrolled in 4 double-blind, placebo-controlled studies of duloxetine in the treatment of SUI (1 phase-2 study in the United States and 3 phase-3 studies performed in 16 countries in Africa, Australia, Europe, and North and South America), details of which have been previously reported.[3,19,20,21] Subjects were randomly assigned to receive duloxetine 40 mg b.i.d. (N = 958) or placebo (N = 955) for 12 weeks. In addition, data were obtained from 4 ongoing uncontrolled longer-term studies of duloxetine 40 mg b.i.d. in 1877 women aged 20 to 87 years. Three of the uncontrolled studies were extensions that followed the 12-week double-blind treatment period in the phase 3 studies; 1 uncontrolled study in 658 women was not preceded by a placebo-controlled study. In total, 2301 women were exposed to duloxetine, with 818 having more than 6 months' exposure and 191 having more than 12 months' exposure.

All women included in the studies met the eligibility criteria for SUI (as defined by IEF recorded on daily diaries, a positive stress pad test, a positive cough stress test, and a simple filling cystometry). This clinical algorithm confirmed the presence of SUI in 92% of the patients when validated against urodynamics.[3]

Information about preexisting conditions and medication was collected using nonprobing questions. Women currently being treated with antidepressants for MDD were excluded. Of the women in the placebo-controlled studies, 1 (0.05%) of 1913 reported a history of bipolar disorder, while 74 (3.87%) of 1913 reported a history of depression. The woman with a history of bipolar disorder did not continue into an open-label longer-term extension study, whereas 45 of the 74 women with history of depression did. In the uncontrolled longer-term studies, 1 (0.05%) of 1877 reported a history of bipolar disorder and 69 (45 + 24) (3.68%) of 1877 reported a history of depression. Treatment groups did not differ significantly by age or ethnic/racial origin in the placebo-controlled studies. Adverse events were elicited by nonprobing inquiry at each visit and were recorded regardless of perceived causality. Treatment-emergent adverse events were registered if they occurred for the first time or worsened during therapy following baseline evaluation. All levels of the safety database, from the patient's wording reported to the investigators to the overall final terms in the *Medical Dictionary for Regulatory Activities* (MedDRA),[9] were searched for matches related to elevated moods.

National or institutional review boards at each study site approved the protocols, and all patients provided signed informed consent prior to study participation.

In one of the placebo-controlled studies,[3] 649 patients completed the Beck Depression Inventory-II (BDI-II) at baseline and at the last postrandomization visit. Each of the 21 questions had 4 categories of suggested answers, and questions included items on mood, self-esteem, energy, sexual activity, and sleep pattern. The BDI-II questionnaire was included in the study to assess whether improvements in quality of life were in fact due to improvements in an unrecognized depressive disorder; the

Table 1. Reported Elevated-Mood Disorders in 1913 Women With Stress Urinary Incontinence Treated With Duloxetine 40 mg Twice Daily or Placebo in Placebo-Controlled Studies

Preferred Term/ Actual Term[a]	Age (y)	Ethnicity	Relationship of Adverse Event to Duloxetine Dose	Relevant History	Relevant Concomitant Medication	Outcome
Mania						
Mania	40	White	Started 2 d after placebo start; stopped before placebo stop date Duration: 3 d	None	None	Subject completed protocol, then entered uncontrolled longer-term study
Euphoric mood						
Euphoria	47	White	Started 7 d after placebo start; event continuing at study discontinuation Duration: > 80 d	None	None	Subject completed protocol, then entered uncontrolled longer-term study
Euphoria	50	White	Started 3 d after duloxetine start; stopped before duloxetine stop date Duration: 57 d	None	None	Subject completed protocol, then entered uncontrolled longer-term study

[a]Preferred term is the MedDRA term; actual term is that used in patient's self-report.
Abbreviation: MedDRA = *Medical Dictionary for Regulatory Activities*.

instrument was not designed to evaluate occurrences of treatment-emergent mania or hypomania.

Statistics

In the randomized controlled studies, Fisher exact test was used to assess the significance of association between elevated moods occurring in women treated with duloxetine versus women treated with placebo. The level of significance was $p < .05$. No statistical analysis was applied to the longer-term studies.

Mean changes in BDI-II scores were analyzed using an analysis of covariance model that included terms for treatment, baseline scores, and baseline incontinence severity. Every subject with at least 1 postbaseline measure was included in the analysis.

RESULTS

Reports of symptoms indicating possible mood elevation were rare and did not occur significantly more often in women treated with duloxetine than in women treated with placebo (Table 1). One woman (0.1%) taking duloxetine in the placebo-controlled studies reported euphoria, compared with 2 women (0.2%) reporting mania or euphoria when taking placebo ($p = .99$). A 40-year-old white woman with no history of mood disorders reported mania 2 days after onset of placebo treatment. This treatment-emergent adverse event lasted 3 days. No women reported hypomania (Table 1).

In the uncontrolled longer-term studies, 6 of 1877 women reported elevated-mood disorders, including a 55-year-old white woman with asthma and climacteric symptoms but no previous history of mood disorders or insomnia, who reported mania 92 days after onset of duloxetine treatment. The event had not resolved at the time she discontinued the study 26 days later due to insomnia. There were 5 occurrences of other symptoms suggesting mood elevation (euphoria, improved disposition, improved temper, and improved mood) (Table 2). No women reported hypomania. Onset and duration of mania and other elevated-mood–related symptoms varied in both the placebo-controlled and the uncontrolled longer-term studies (Tables 1 and 2). Of the 7 duloxetine-treated women reporting mania, euphoria, or other elevated moods, 2 had a history of insomnia (Tables 1 and 2); 1 discontinued because of aggravated insomnia. Overall, no women discontinued because of elevated moods.

Hydroxyzine (for anxiety) and zolpidem tartrate (a hypnotic agent) were used concomitantly by 2 of the women who reported symptoms suggestive of mood elevation (Table 2). The 34-year-old Hispanic woman who took zolpidem tartrate discontinued the study because of aggravated insomnia.

Mean BDI-II scores did not differ at baseline between duloxetine- and placebo-treated subjects. Only 24 (3.6%) of 666 subjects had appreciable symptoms of depression based on a BDI-II score of 17 or greater at baseline. In these women, duloxetine-treated subjects had a mean decrease of 8.2 points in their BDI-II scores from baseline to postbaseline compared with a 5.4-point decrease in placebo subjects ($p = .46$). Although this difference was not statistically significant, the small number of subjects provided very little statistical power for this comparison. Subjects without appreciable symptoms of depression (baseline BDI-II score < 17) had no significant change from baseline to endpoint in their BDI-II scores (mean change, duloxetine = +.26 vs. placebo = +.20 points, $p = .68$).

DISCUSSION

Duloxetine does not seem to induce mood elevation, as measured by the few reports of symptoms such as mania and euphoria, when used for the treatment of SUI in women. One case of mania was reported in the placebo-treated group while 1 case of mania was reported in the uncontrolled longer-term studies. No cases of hypomania

Table 2. Reported Elevated-Mood Disorders in 1877 Women With Stress Urinary Incontinence Treated With Duloxetine 40 mg Twice Daily in Uncontrolled Longer-Term Studies

Preferred Term/ Actual Term[a]	Age (y)	Ethnicity	Relationship of Adverse Event to Duloxetine Dose	Relevant History	Relevant Concomitant Medications	Outcome
Mania						
Manic	55	White	Started 92 d after duloxetine start; event continuing at study discontinuation Duration: > 26 d	None	None	Discontinued due to adverse event (sleeplessness)
Euphoric mood						
Euphoria	34	Hispanic	Started 6 d after duloxetine start; stopped before duloxetine stop date Duration: 30 d	Occasional insomnia	Zolpidem tartrate (nonbenzodiazepine hypnotic); initiated before reporting euphoria	Discontinued due to adverse event (severe insomnia)
Elevated mood						
Improved disposition	43	White	Started 15 d after duloxetine start; stopped before duloxetine stop date Duration: 321 d	None	Decongestant during 3 d; initiated 20 d after reporting elevated moods	Discontinued due to lack of efficacy (patient perception)
Improved temper	45	White	Started 18 d after duloxetine start; stopped before duloxetine stop date Duration: 49 d	None	Hydroxyzine (antihistamine with antidepressant activity); initiated 19 d after reporting elevated moods	Discontinued due to adverse event (genital itch)
Improved mood	44	White	Started 11 d after duloxetine start; stopped before duloxetine stop date Duration: 241 d	None	Pseudoephedrine; initiated before reporting elevated moods	Discontinued due to lack of efficacy (patient perception)
Improved disposition	49	White	Started 12 d after duloxetine start; event continuing at study discontinuation Duration: > 206 d	Insomnia	Chlorpheniramine maleate and meclizine (antihistamines); pseudoephedrine; all agents initiated before reporting elevated moods	Discontinued due to lack of efficacy (patient perception)

[a]Preferred term is the MedDRA term; actual term is that used in patient's self-report.
Abbreviation: MedDRA = *Medical Dictionary for Regulatory Activities*.

were reported in any studies. Of all 2301 women treated with duloxetine during placebo-controlled or uncontrolled longer-term studies, 1 woman (0.04%) reported mania and 6 women (0.26%) reported other mood disorders, but no women discontinued due to mood elevation (Tables 1 and 2). Few women who did experience mood-related symptoms were taking concomitant psychiatric medications.

One of the limitations of analyses of this type is accuracy of diagnosis as it relates to both the reported symptoms and the interpretation by the different investigators. Figures for the incidence of mania and hypomania were based on patient-reported adverse events, which were then mapped to standard MedDRA terms, rather than a diagnosis made by a psychiatrist experienced in identifying such disorders. As a consequence, it is open to question whether patients who reported mania, hypomania, or other manifestations of mood disorder would in fact have met diagnostic criteria using traditional methods. As an example, a diagnosis of mania requires the presence of a number of specific symptoms and a significant degree of functional impairment (frequently culminating in a hospital admission). The patient in this analysis reported as suffering from mania was able to continue in the study, making it highly unlikely that she would have met the criteria for a full-blown manic episode. Notwithstanding this limitation, the use of patient-reported adverse events still provides a useful indication of the prevalence of drug-related alterations in mood within the studies described, and this analysis indicates that such reports were extremely uncommon in the population studied.

It is not possible to comment specifically on the impact of duloxetine treatment on the mood of women with SUI who also had a concurrent diagnosis of depression or bipolar disorder, since very few reported these disorders and past psychiatric history was not systematically gathered from patients in the included studies. As with other antidepressants, a possible concern might be that women with undiagnosed bipolar disorder prescribed duloxetine for SUI could theoretically be placed at an increased risk of an episode of mania or hypomania. The coexistence of bipolar disorder and stress urinary incontinence in the same patient is possible. Although bipolar disorder is less prevalent in the general population than MDD, estimates of a lifetime prevalence of between 0.8% and 1.6%[10] are almost certainly an underestimate. As previously stated, a review of the relevant literature suggests that the risk of a switch into mania in bipolar patients treated with antidepressants is between 3.7% and 11.2%.[8] Critically, however, this risk is significantly dependent on the class

of antidepressant studied, with selective serotonin reuptake inhibitors (SSRIs) carrying no greater risk of switch than placebo but the older tricyclic antidepressants (TCAs) seemingly associated with a significantly higher risk (11.2%). Data are not available on the risk of manic switch with duloxetine in bipolar disorder, nor are they available for the most similar marketed SNRI antidepressant (venlafaxine). In patients with major depression treated with duloxetine in placebo-controlled studies, 1 case of mania (0.1%) occurred in the placebo-treated patients, and 2 cases of hypomania (0.2%) were observed in the duloxetine-treated patients.[11] (In premarketing unipolar depression trials with venlafaxine, mania or hypomania occurred in 0.5% of venlafaxine-treated patients compared with 0% of placebo patients.)[18] Venlafaxine is not indicated for the treatment of SUI.

There are currently no data to suggest an increased risk of mood elevation resulting from drug-drug interactions between duloxetine and other drugs. Tolterodine, a drug indicated for the treatment of overactive bladder and urge incontinence, is metabolized by hepatic cytochrome CYP2D6. Duloxetine is a substrate and modest inhibitor of CYP2D6.[12] A drug-drug interaction study with duloxetine and tolterodine was conducted in 3 healthy male and 13 female volunteers aged 21 to 65 years.[12] During a 5-day period, duloxetine 80 mg/day and tolterodine 4 mg/day were coadministered. None of the 16 healthy volunteers reported any symptoms of mood elevation.

Drug-drug interaction studies in other small samples have not indicated an increased risk of mania or hypomania in healthy subjects receiving duloxetine together with another antidepressant. A drug-drug interaction study of duloxetine and paroxetine was conducted in 12 healthy male volunteers aged 21 to 27 years.[13] During a 7-day period, duloxetine 40 mg/day and paroxetine 20 mg/day were coadministrated until steady state was reached. None of the 12 men reported any symptoms of mood elevation. Similarly, a drug-drug interaction study of duloxetine and desipramine was conducted in 7 healthy male and 9 female volunteers aged 18 to 65 years[13] in which a single dose of desipramine 50 mg was added to steady-state duloxetine 60 mg b.i.d. None of the subjects reported elevated moods when desipramine was added.

Several studies have reported comorbidity between depression and UI, but this association seems to be related to urge urinary incontinence and not SUI.[14–17] Since women currently being treated with antidepressants were excluded, the population studied in this review seems therefore representative of a female population without obvious depression.

In conclusion, the use of duloxetine as a treatment for SUI in women does not seem to induce mania or hypomania in this population, in which few women had history of bipolar disorder or depression and women on antidepressants were excluded. As with other marketed drugs effective in the treatment of major depressive disorder, duloxetine should be used with caution in patients with a history of mania.

Drug names: desipramine (Norpramin and others), duloxetine (Cymbalta), hydroxyzine (Vistaril, Atarax, and others), meclizine (Antivert and others), paroxetine (Paxil and others), tolterodine (Detrol), venlafaxine (Effexor), zolpidem (Ambien).

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