An 8-Week, Open-Label Trial of Duloxetine for Comorbid Major Depressive Disorder and Chronic Headache

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Background: Although major depression and chronic headache are strongly associated, there is insufficient evidence for the use of antidepressants for this specific comorbidity. This trial aimed to investigate the efficacy and tolerability of duloxetine for this indication.

Method: Thirty outpatients with DSM-IV major depressive disorder and concurrent primary chronic headache (chronic migraine, chronic tension-type headache, or both), 18 to 55 years old, were recruited from April 2006 to March 2007, if they scored > 21 on the Montgomery-Asberg Depression Rating Scale (MADRS) and had no other significant clinical condition. Subjects received duloxetine 60 mg/day for 8 weeks. Scores on the MADRS and a visual analog pain scale (VAS) were the co-primary outcome measures. Scores on the brief version of the World Health Organization Quality of Life scale (WHOQoL-BREF) and number of headache days/week were secondary outcome measures. The study was conducted at the Liaison-Psychiatry Service of SOCOR General Hospital, Belo Horizonte, Brazil.

Results: Mean ± SD MADRS scores decreased significantly from baseline to endpoint (29.5 ± 5.2 to 8.9 ± 8.7 points, $p < .001$), and mean ± SD VAS scores decreased significantly from 5.8 ± 1.9 to 1.9 ± 2.5 points ($p < .001$). Combined intent-to-treat response rate (> 50% reduction on MADRS and > 40% on VAS) was 66.7% (20/30). Significant improvements in both headache and depression were evident after the first week. Mean ± SD WHOQoL-BREF scores increased (improved) 18.8 ± 21.9 points ($p < .001$), and mean ± SD number of headache days/week decreased from 5.2 ± 2.0 to 2.9 ± 2.5 days/week ($p < .001$). Two subjects discontinued for side effects and 3 for nonadherence.

Conclusion: In this preliminary open trial, duloxetine 60 mg/day was effective, fast acting, and well tolerated for the treatment of comorbid major depressive disorder and chronic headache.

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Severe and chronic headache is very commonly present during major depressive episodes (up to 50% prevalence).[1,2] Female sex and depression severity and chronicity are associated with the co-occurrence of headache.[3] On the other hand, major depression occurs in about 50% to 60% of chronic primary headache patients, including those with migraine and tension-type headache.[3,4] Cohort studies have shown a bidirectional relationship between depression and migraine: a diagnosis of major depression is associated with a higher risk of developing first-onset migraine (odds ratio [OR] = 3.4), and migraine predicts the incidence of first-onset major depression (OR = 5.8) over the course of 2 years.[5]

The comorbidity of depression and headache also has prognostic consequences. The occurrence of somatic symptoms in depression leads to greater functional disability,[6] and antidepressant response is reduced by the presence of migraine.[7] Conversely, there is preliminary evidence that among patients with chronic headache, those who are depressed improve more than those who are not depressed when treated with antidepressants.[8]

Antidepressants are twice as likely to produce improvement in chronic headache patients as placebo.[9] The most robust results, however, favor tricyclic compounds, which may produce considerable adverse effects and clinically significant drug interactions when used at the higher doses needed to treat depression. There is conflicting evidence for the effectiveness of selective serotonergic agents for chronic headache,[9] but the selective serotonin and norepinephrine reuptake inhibitors venlafaxine and mirtazapine have shown some promising results.[10–12] Despite the clinical relevance and the need for safe and effective treatments, to our knowledge, only 1 clinical trial[13] has been published supporting the use of antidepressants (namely, amitriptyline and citalopram) specifically in patients with comorbid major depression and chronic headache.

Duloxetine is a balanced selective serotonin and norepinephrine reuptake inhibitor that has proven efficacy in major depressive disorders.[14,15] Duloxetine significantly improves painful physical symptoms in major depressed patients,[16,17] and has also been shown to be useful for fibromyalgia with or without major depression[18] and for neuropathic pain.[19]

This trial was designed to investigate the efficacy, safety, and tolerability of duloxetine in treating comorbid syndromes of DSM-IV major depressive disorder and chronic headache.

METHOD

We conducted an 8-week, open-label trial of duloxetine for patients with comorbid major depressive disorder and chronic headache at the Liaison-Psychiatry Service of SOCOR General Hospital, Belo Horizonte, Brazil. Patients were mostly referred from other clinicians and neurologists. The inclusion period started in April 2006 and ended in March 2007.

We included patients from both sexes, 18 to 55 years old, with a diagnosis of major depressive disorder according to DSM-IV criteria and based on the Mini International Neuropsychiatric Interview (MINI),[20] with Montgomery-Asberg Depression Rating Scale (MADRS) scores greater than 21, who also met the International Headache Society criteria for chronic primary headache (International Classification of Headache Disorders-2 codes 1.5.1, 1.6.1, 2.3.1, 2.3.2, and 2.4.3).[21] As a whole, the diagnoses of chronic primary headache require that a patient have had headache episodes at least 15 days per month for 3 consecutive months but without a frequent use of analgesic drugs (which would indicate a probable secondary headache diagnosis). All subjects gave their written, informed consent, and the trial was approved by the local ethics committee. Subjects were excluded if they had a greater than 50% reduction on MADRS scores during the washout period, had a history of illicit drug or alcohol dependence, had multiple allergies or hypersensitivity to duloxetine, had a history of epilepsy or significant neurologic disorder, constituted a significant suicide risk, were pregnant or lactating, were sexually active female subjects not using an efficient contraceptive method, had significant laboratory abnormalities at baseline, had significant clinical disease, or if they met DSM-IV criteria for somatization disorder (300.81) or presented with delusional pain symptoms.

Eligible subjects started a 1-week washout period during which laboratory tests were performed. Subjects entering this protocol were prescribed fixed-dose duloxetine 60 mg, once daily, preferably at nighttime in order to lessen sensitivity to eventual gastrointestinal side effects. They were then evaluated at 5 subsequent visits at weeks 1, 2, 4, 6, and 8. Clinical assessment of adverse events and drug compliance was performed at each subsequent visit. Patients were asked to return the medication packages so that remaining pills could be counted to assess adherence to study protocol. Nonadherence, for this study, was defined as (1) failure to use at least 80% of the prescribed medication for the total study period, or (2) intentional and repetitive use of doses of the study drug larger than prescribed. Permitted concomitant medications included anxiolytics (benzodiazepines, up to 10 mg diazepam or equivalents daily, only if subjects were already taking them before entering the study), rescue pain medication (only paracetamol was allowed, maximum 2250 mg/wk), and antihypertensive drugs when they were already in use before entering the protocol.

Primary efficacy measures were scores on the MADRS and the Visual Analog Scale (VAS) for pain assessment.

The MADRS has been thoroughly used for the assessment of clinical changes in depressive states along the course of antidepressive treatments. A Brazilian version is available and has been validated.[22] For this study, the MADRS was preferred because it does not include many somatic or psychomotor items. Thus, the change in MADRS scores along the course of treatment would not be confounded by changes in somatic symptom instruments.

The VAS is a simple and intuitive instrument for the assessment of pain, widely used in headache clinical trials. Subjects were instructed to indicate the intensity of pain in the previous week by marking a 100-mm line anchored with terms describing the extremes of pain intensity. In the assessment of chronic pain, the VAS is superior to fixed interval scales, relative pain scales, and verbal reports of pain.[23]

Secondary efficacy measures included information obtained from subjects' headache diaries (number of headache episodes, and duration) and scores on the brief version of the World Health Organization Quality of Life scale (WHOQoL-BREF). The latter is a 26-item cross-cultural and self-administered instrument for the assessment of quality of life dimensions (physical health, psychological health, social relationships, and environment). It has been translated and validated for use in Brazilian patients with major depression.[24]

Safety Measures

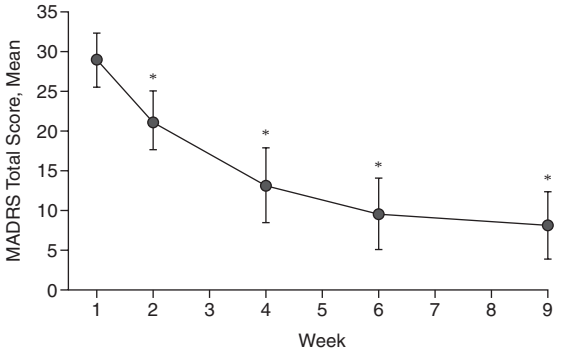
Spontaneously reported adverse events and weight were recorded at each visit. Clinical laboratory tests (complete blood count, creatinine, fasting glucose, and beta-human chorionic gonadotropin for women) were obtained at screening and at the end of study treatment. Heart rate and systolic and diastolic supine blood pressure were obtained at each visit. Clinically significant findings or serious adverse events (death, need for hospitalization, or life-threatening medical events) would lead to termination of subject's participation in this trial.

Table 1. Baseline Characteristics of 30 Patients With Comorbid Major Depressive Disorder and Chronic Headache

Characteristic	Value
Sex, female, N (%)	28 (93.3)
Age, mean ± SD, y	41 ± 8
Marital status, N (%)	
Married/living with partner	22 (73.3)
Single	3 (10.0)
Divorced	5 (16.7)
Type of major depression, N (%)	
Recurrent	14 (46.7)
Single episode	16 (53.3)
Type of chronic headache, N (%)	
Migraine	6 (20.0)
Tensional	12 (40.0)
Mixed	12 (40.0)
Baseline BMI, mean ± SD	26.5 ± 5.2
Baseline MADRS score, mean ± SD	29.5 ± 5.2

Abbreviations: BMI = body mass index, MADRS = Montgomery-Asberg Depression rating scale.

Figure 1. Time Course of Improvement in Mean Change of MADRS Total Score in Patients With Comorbid Major Depressive Disorder and Chronic Headache[a]



[a]Error bars represent SD.
*p < .001 relative to baseline values.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Statistical Analyses

All analyses were carried out on an intent-to-treat basis (all subjects taking at least 1 dose of the study medication). Longitudinal efficacy outcomes (MADRS, VAS, and WHOQoL BREF scores and number of headache days/week) were analyzed using paired t tests comparing baseline and last-observation-carried-forward (LOCF) results, with α set at .05, 2-tailed.

We defined treatment response for major depressive disorder as a > 50% reduction in MADRS scores and for chronic headache symptoms as a > 40% reduction in VAS scores for pain at last visit (LOCF). Remission from depression was defined as achieving MADRS scores < 10 at last visit (LOCF).

Subjects who were responsive and nonresponsive to the drug trial were compared by their baseline characteristics and adjuvant medication use with binary logistic regression models. The same models were used to make comparisons between completers and noncompleters of the study protocol.

RESULTS

Thirty patients with DSM-IV comorbid major depressive disorder and chronic headache entered the trial with duloxetine. One eligible subject did not return after the baseline visit and was replaced. Baseline characteristics of the sample are described in Table 1.

Main Outcome Statistics

Mean ± SD MADRS scores at baseline were 29.5 ± 5.2, and 8.9 ± 8.7 points at last visit (LOCF; Figure 1). Mean ± SD differences between baseline and endpoint were 20.7 ± 8.6 points ($p < .001$). Twenty-two subjects were responsive to duloxetine, yielding a 73.3% response rate for depression scores. Seventeen subjects achieved a MADRS score < 10 at last visit (LOCF), yielding a 56.7% remission rate for depression.

Mean ± SD baseline VAS scores were 5.8 ± 1.9 points, and at last visit (LOCF) they reached 1.9 ± 2.5 points (Figure 2). Mean ± SD differences between baseline and endpoint were 4.0 ± 2.7 points ($p < .001$). Twenty-two subjects had a reduction in VAS scores greater than 40%, yielding a 73.3% response rate. Moreover, 41.3% of the subjects achieved VAS scores of 3 mm or lower (on a 100 mm scale) at the end of study participation.

Twenty patients achieved response criteria on both depression and pain scores, with a combined response rate of 66.7%.

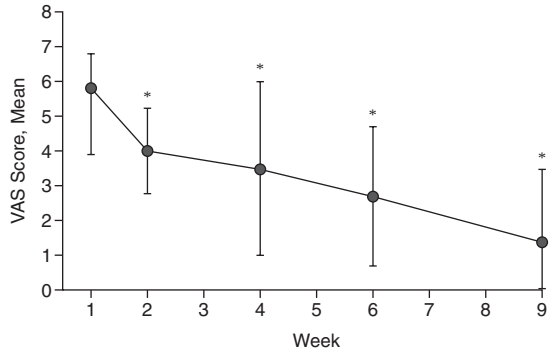
Mean ± SD baseline scores on the WHOQoL-BREF scale were 65.4 ± 13.1 points, and at last visit (LOCF), scores increased (improved) to 82.3 ± 21.2 points (Figure 3). Mean ± SD differences between baseline and endpoint were 18.8 ± 21.9 ($p < .001$).

Before entering the study protocol, patients had been suffering headache episodes for at least 15 days per month for the previous 3 months (inclusion criteria). The headache diary was given to the subjects on the first day of active treatment. The mean ± SD number of headache days per week recorded in the diary was 5.2 ± 2.0 after the first week of treatment, and at the last week it decreased to 2.9 ± 2.5 days ($p < .001$). Diary data for headache duration were considered imprecise for many subjects, despite our efforts to educate them on this procedure, so we decided not to consider this information in further analyses.

Onset of Response

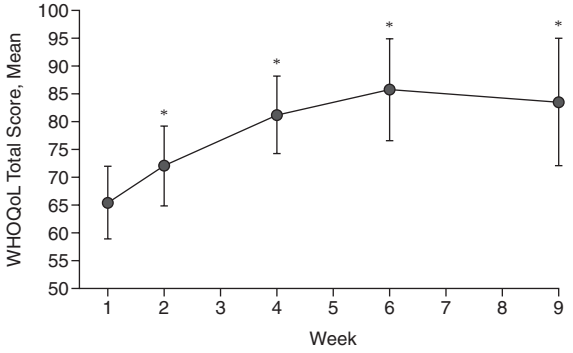
In order to evaluate the speed of response to duloxetine, MADRS and VAS scores were compared between

Figure 2. Time Course of Improvement in Mean Change of VAS Score in Patients With Comorbid Major Depressive Disorder and Chronic Headache[a]



[a]Error bars represent SD.
*p < .007 relative to baseline measures.
Abbreviation: VAS = visual analog scale.

Figure 3. Time Course of Improvement in Mean Change of WHOQoL-BREF Total Score in Patients With Comorbid Major Depressive Disorder and Chronic Headache[a]



[a]Error bars represent SD.
*p < .001 relative to baseline measures.
Abbreviation: WHOQoL-BREF = World Health Organization Quality of Life scale-brief version.

the first day of medication and the subsequent visits. Promptly at 1 week after starting medication, a 28% mean ± SD reduction on the VAS scores (1.64 ± 2.8 decrease; p = .007) and also a significant 27% mean ± SD reduction in MADRS scores (8.0 ± 5.9 decrease, p < .001) were observed.

Safety and Tolerability

Adverse effects, as spontaneously reported by subjects, are summarized in Table 2. Nausea was the most common of these but in most cases was limited to the first 3 to 6 days of treatment. When subjects reported insomnia, they were asked to take duloxetine capsules in the morning instead of at night, and this procedure generally improved tolerability. No serious adverse events were reported in this study.

Table 2. Adverse Effects of Duloxetine 60 mg/day, With Frequencies Greater Than 10% in 30 Patients With Comorbid Major Depressive Disorder and Chronic Headache

Adverse Effect	N	%
Nausea	19	63.3
Insomnia	9	30.0
Diurnal somnolence	8	26.7
Reduced appetite	7	23.3
Vomiting	5	16.7
Diarrhea	4	13.3
Dizziness	4	13.3
Increased sweating	3	10.0

Five patients failed to comply with the study protocol and stopped using duloxetine before the 8-week study period had ended. The dropout rate was 16.7%. Only 2 patients abandoned the protocol because of adverse events, namely, nausea, vomiting, dizziness, tremor, and insomnia. The other 3 subjects dropped out because of nonadherence. These 5 subjects who dropped out remained in the protocol for a mean ± SD duration of 29.8 ± 20.2 days.

Subjects entered the study weighing a mean ± SD 68.5 ± 15.4 kg, and at last visit (LOCF) there were no statistically significant weight changes (69.1 ± 16.1 kg).

Mean ± SD systolic blood pressure was 124.8 ± 21.8 mm Hg, diastolic blood pressure was 83.0 ± 12.9 mm Hg, and heart rate was 77.1 ± 8.8 bpm at baseline. Again, no significant changes were seen at last visit (LOCF): mean ± SD systolic blood pressure was 124.0 ± 22.8 mm Hg, diastolic blood pressure was 83.6 ± 13.6 mm Hg, and heart rate was 78.7 ± 9.8 bpm.

Also, no statistically significant changes were seen between baseline and endpoint laboratory evaluations.

Influence of Headache Type

Although subjects with tension-type, migraine, or mixed headache had statistically similar baseline scores on the MADRS and VAS, and all 3 groups did show significant responses to duloxetine, the mixed headache group achieved more modest results. The mean ± SD differences in MADRS scores between baseline and last visit (LOCF) were 14.9 ± 9.1 points for mixed, 24.2 ± 2.0 points for migraine, and 23.9 ± 8.0 points for tension-type headache (p = .02). Similarly, mean ± SD differences in VAS scores were 2.5 ± 2.3 points, 5.7 ± 2.1 points, and 4.4 ± 2.8 points, respectively (p = .04).

Responsive vs. Nonresponsive Patients

Twenty subjects who achieved a combined response to depression and headache (MADRS and VAS scores) were compared to the 10 nonresponsive subjects, according to baseline characteristics. Age (p = .59), MADRS scores (p = .33), VAS scores (p = .67), and BMI (p = .68) did not predict clinical response in this study.

The use of analgesics did not significantly influence responsiveness to either depression or pain, although there was a trend for nonresponsive subjects to use higher mean ± SD doses of paracetamol during the study period than responsive subjects (9500 ± 10750 mg vs. 3630 ± 4275 mg, respectively, p = .053). Although there was no information on patients' frequency of use of analgesics before starting duloxetine, a mean ± SD reduction in the use of paracetamol was observed when there was a combined response to depression and pain (from 869 ± 1393 mg at the first week of treatment to 324 ± 502 mg at last visit LOCF), as well as for nonresponsive subjects (from 1375 ± 1247 mg at the first week of treatment to 810 mg ± 863 at last visit [LOCF]).

The use of adjunctive benzodiazepines (N = 10, p = .261) and beta-blockers (N = 5, p = .459) was not statistically associated with response for either depression or pain and had been started prior to enrolling, so it had no influence on results.

Completers vs. Noncompleters

Subjects who failed to comply with protocol after study entry and dropped out (noncompleters) were compared to completers regarding baseline characteristics: age (p = .60), MADRS scores (p = .14), VAS scores (p = .11) and BMI (p = .72). None of these variables predicted study completion.

DISCUSSION

Open-label studies tend to report superior results compared to randomized, controlled trials for depression and pain. This disparity is thought to be related to a confusion of the actual therapeutic benefits of medication and placebo effects, which cannot be ruled out in an uncontrolled design. Because of the lack of a comparator group, statistical comparisons could only be made relative to baseline values. Male subjects were underrepresented in our sample (N = 2). These aspects of the study design and the small sample size impose care when interpreting and extrapolating the current outcome results. With these limitations in mind, we will discuss the main results, comparing them whenever possible with those of previous reports.

In the current study, response and remission rates to duloxetine for depressive symptoms were slightly higher than those reported in randomized, controlled trials (73% vs. 62%–65% and 57% vs. 43%–56% respectively).[15,25,26] Response rates for headache in our study were slightly higher (73% vs. 50%–65%) than those reported for other studies of duloxetine in chronic pain, namely fibromyalgia[18,27] and neuropathic pain.[19] Altogether, those results indicate that the analgesic effects of duloxetine are neither specific to headache nor restricted to depressed patients.

This is the first study reporting on the efficacy of duloxetine in the treatment of headache. The original trials of duloxetine had shown efficacy for every painful physical symptom of depression except headache.[25,26,28] Moreover, emergent headache has been previously reported as a quite frequent side effect (circa 20%).[29] When selecting patients specifically with chronic primary headache, this study has approached headache differently, not merely as a subsymptom of depression but as a separate and severe concomitant condition, thus enhancing the sensitivity to pain outcome measures. This approach may explain the more evident analgesic benefit in headache observed in our study when compared to previous protocols. Controlled trials using other dual-acting antidepressants, venlafaxine (44%)[12] and mirtazapine (45%),[11] for chronic headache showed more modest response rates than ours. However, comparisons of outcome measures between studies may also be biased by other differences in study design and patient selection strategies.

A putative mechanism of action of duloxetine in both chronic headache and major depression involves the modulation of serotonin and norepinephrine neurotransmission in the brain and spinal chord.[30] The main hypothesis for the concomitant effect of monoamine reuptake inhibitors in major depression and chronic headache implies the existence of a common etiologic substrate for both disorders that shares abnormalities in monoaminergic neurotransmission and a tendency for neural sensitization.[31,32] The similar response rates for both chronic tension-type headache and migraine suggest that the analgesic effects are not exclusively associated with muscle tension relaxation and could be related to the regulation of central pain modulation circuits.

A remarkable finding in this trial was the very fast onset of action on depressive and headache symptoms, both with clinically significant relief after one week of treatment. This finding must be contrasted with the quite long-term evolution of chronic headache, which in some subjects exceeded 3 years. Although previous studies have reported that duloxetine usually requires at least 2 weeks for the onset of antidepressant response,[29,33] a recent study specifically assessing onset of response showed that both duloxetine and escitalopram statistically differed from placebo after the first week of treatment.[34] Also consistent with our findings, very fast analgesic effects of duloxetine have been consistently reported for other painful conditions.[18,19,25,27,35] A placebo effect could have influenced onset of response and cannot be ruled out. However, the current study selected a very specific sample of chronic headache patients that could respond to duloxetine in a particularly rapid way, as a function of its fast improvement in pain and health-related quality of life, in comparison with the samples of general depressive patients included in other reports.

Gastrointestinal adverse effects were very frequent in this sample (63.3%), although most cases were of short duration (< 1 week) and easily overcome. The frequent

use of nonsteroidal analgesics for headache could account for some of the excess emerging gastrointestinal symptoms, when compared to previous trials of duloxetine for noncomorbid major depression (< 40%).[36,37] This study was designed before the commercial availability of duloxetine 30 mg. Starting with lower doses of duloxetine has been described as a sound strategy for reducing treatment-emergent nausea.[36]

CONCLUSIONS

In this open trial, duloxetine at 60 mg daily doses was effective, fast acting, and well tolerated for the treatment of comorbid major depressive disorder and chronic headache, regardless of headache type.

The results of this study should be considered preliminary evidence, and double-blind, randomized, controlled trials are warranted to confirm these findings.

Drug names: citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), mirtazapine (Remeron and others), venlafaxine (Effexor and others).

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