

## Milnacipran in the treatment of bulimia nervosa: a report of 16 cases

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Received 7 June 2002; accepted 10 September 2002

### Abstract

Controlled trials in patients with bulimia nervosa have demonstrated efficacy of antidepressant medications with serotonergic function (e.g. fluoxetine) as well as noradrenergic function (e.g. desipramine). Sixteen out-patients with bulimia nervosa according to DSM-IV criteria were treated in a drug surveillance with 100 mg of milnacipran, a specific serotonin and noradrenaline reuptake inhibitor (SNRI). Ten patients completed the 8-week observation period. The reasons for premature attrition were improvement in one patient (no. 12), a generalized exanthema in one patient (no. 7), severe nausea in one patient (no. 8) and non-compliance due to non-drug-related reasons in three patients (no. 1, 2, and 16). An intent-to-treat analysis exhibited a significant reduction in weekly binge eating and vomiting frequency from baseline to the end of treatment. Three patients stopped binge eating and purging completely during the last week of treatment. Furthermore, there was a concomitant decrease of depression ratings (HAMD, BDI). Our preliminary data give rise to the notion that milnacipran may be promising in the treatment of bulimia nervosa.

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*Keywords:* Bulimia nervosa; Treatment; Milnacipran; Serotonin and noradrenaline reuptake inhibitor

### 1. Introduction

From a neurobiological perspective, research suggests that the serotonergic system may play an important role in the pathophysiology and perhaps etiopathogenesis of eating disorders. Disturbances of brain serotonin activity have been described in acutely ill as well as long-term recovered patients with bulimia nervosa (Goldbloom et al., 1990; Brewerton et al., 1992; Levitan et al., 1997; Jimerson et al., 1997; McBride et al., 1991; Monteleone et al., 1998; Smith et al., 1999; Tauscher et al., 2001). There is evidence for an impaired serotonergic responsiveness which largely but not entirely seems to normalize following remission (Wolfe et al., 2000; Kaye et al., 1998; Weltzin et al., 1994, 1995; Oldman et al., 1995).

However strong the link between eating disorders and

serotonergic activity seems to be, it is unlikely that a specific dysfunction of one neurotransmitter system can fully explain the pathogenesis of bulimia nervosa. There is also evidence, although less strong, for a disturbance of noradrenergic function in normal-weight bulimic subjects (Kaye et al., 1990; Pirke, 1996).

There is a substantial body of literature demonstrating that MAO inhibitors, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs) are effective in treating patients with bulimia nervosa (BN) (Lennkh et al., 1997; Fichter, 1993; Walsh et al., 1997). It seems possible that antidepressants correct a disturbance of monoaminergic function in patients with eating disorders. Among the SSRIs, fluoxetine has been investigated most extensively and has demonstrated a significant superiority over placebo in reducing binge eating and vomiting frequency. In addition, fluoxetine has a favorable side-effect profile (FBNC study group, 1992; Goldstein et al., 1995). Other SSRIs like fluvoxamine, paroxetine, citalopram, and sertraline seem to have a similar efficacy in patients with

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eating disorders, however have not been studied to the same extent as fluoxetine.

Even though SSRIs are currently recommended as the first-line pharmacological treatment in BN, antidepressants with noradrenergic activity also are effective in BN. Imipramine (Agras et al., 1987) and desipramine were found to be significantly superior to placebo in reducing binge eating and purging frequencies and in improving the associated psychopathology in short-term treatment studies. Desipramine is a tricyclic secondary amine antidepressant with preferential affinity for the noradrenergic reuptake sites. In double-blind, placebo-controlled studies with desipramine, the reduction in binge eating frequencies ranged from 40 to 90% (Hughes et al., 1986; Barlow et al., 1988; Blouin et al., 1988; Walsh et al., 1991). The tricyclic antidepressant desipramine has a number of pharmacodynamic properties additionally to the noradrenergic one, which are linked to burdensome side effects, specifically for the necessary long-term outcome. In this line, high drop out rates—up to 50%—have been reported in studies employing desipramine, which were mainly due to side effects (Leitenberg et al., 1994; Barlow et al., 1988; Walsh et al., 1991; Agras et al., 1992).

We recently published the results of a drug surveillance using 8 mg of reboxetine, a novel selective noradrenaline reuptake inhibitor in seven patients with bulimia nervosa (El-Giamal et al., 2000). The monthly binge eating frequency showed a reduction of 73% and the frequency of vomiting episodes per month decreased by 67%. The only clinically relevant adverse effect was constipation which led to early attrition in two patients.

The present drug surveillance intended to measure the efficacy and tolerability of milnacipran in the short-term treatment of patients with BN. Milnacipran is a dual acting antidepressant which inhibits the reuptake of both serotonin and noradrenaline with approximately equal potency with no effect on the reuptake of dopamine and no action at any pre- or postsynaptic receptors (Montgomery et al., 1996). It is rapidly absorbed when taken orally, has an intermediate half-life of about 8 h and no active metabolite. It does not modify, and is not affected by, the cytochrome P450 system (for review see Briley, 1998). Data from placebo-controlled trials and the results of comparator studies involving TCRs and SSRIs have confirmed that milnacipran is an effective and well-tolerated antidepressant, particularly useful in patients with severe depression (Kasper, 1997; Kasper et al., 1996).

## 2. Experimental procedures

Sixteen female out-patients with bulimia nervosa (BN) were included. All patients were purgers, 15 patients vomited regularly and three patients abused laxatives.

Patients were excluded if they had taken any psychotropic medication or had received psychotherapy for bulimia nervosa in the preceding 4 weeks, if they had clinically significant medical illness or a history of substance abuse.

Diagnosis was made according to the criteria outlined in the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV, American Psychiatric Association, 1995). All subjects underwent the Structured Clinical Interview (German version of the SCID, Wittchen et al., 1997) to assess current and past psychiatric disorders including bulimia. Subjects completed the German version of the Eating Disorder Inventory (EDI-2, Thiel et al., 1997). The prevalence of affective symptoms was rated using the 21-item Hamilton Depression Rating scale (HAMD, Hamilton, 1967) and the Beck Depression Inventory (BDI, Beck et al., 1961).

The investigators kept weekly records of the Clinical Global Impression (CGI, National Institute of Mental Health, 1976). Adverse events were recorded weekly by active questioning using a scale with a range from 0 (not present) to 3 (severe). For the pretreatment assessment of binge eating and purging behavior, the patients filled out the Eating Disorders Questionnaire (EDQ, Mitchell et al., 1985). The patients completed daily records of bingeing and purging episodes throughout the 8 weeks. They were asked to report binges, that were defined as 'eating definitely more than a normal meal, combined with loss of control and guilt feelings'. No difference between objective versus subjective binges was made.

Binge eating and purging frequencies can fluctuate considerably in the short-term, suggesting that a 1-week window may not capture the overall pattern of change. Therefore, in completers a period of 4 weeks was chosen in addition to a 1-week period to evaluate changes in binge eating and purging frequencies.

Milnacipran was administered orally 50 mg daily for the first 3 days and 100 mg daily (b.i.d.) for the following weeks. Patients were seen by a psychiatrist once a week for the first 4 weeks, and then every other week for the last 4 weeks.

Wilcoxon matched-pairs signed ranks tests were used to assess differences between baseline and post-treatment with  $P < 0.5$  as the defined level of significance. All patients were included in an intent-to-treat analysis based on the last observation carried forward for patients not completing the trial. In addition, a completer analysis for the 10 patients who finished the whole treatment period was carried out.

Percentage change in binge eating and vomiting episodes per week from baseline to endpoint were evaluated in each patient. A clinical response to therapy was defined as at least 50% reduction in bulimic episodes (binge eating and purging) from baseline to the patients' last visit.

All analyses were performed using SPSS for Windows, V.6.1.3.

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