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Preliminary communication

Is treatment-associated hypomania rare with duloxetine: Secondary analysis of controlled trials in non-bipolar depression

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Abstract

Background: Selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors (SNRIs) like duloxetine have the efficacy of tricyclic antidepressants (TCAs) with a more tolerable side-effect profile. Bipolar disorder is often undetected, with the most common misdiagnosis being unipolar depression. Studies have suggested that treatment of bipolar and unipolar depression with heterocyclic TCAs may increase the risk of switch rate to mania. Studies of antidepressants in unipolar major depression show a small risk of mania or hypomania, presumably because some bipolar depressives were mistakenly studied. This study investigated the rate of hypomania, mania, and hypomanic-like symptoms observed during treatment with duloxetine in patients with major depression.

Methods: This was a retrospective analysis of data from eight placebo-controlled, double-blind, randomized clinical trials of duloxetine in patients with non-bipolar major depression.

Limitations: The studies were of limited duration. Manic or hypomanic symptoms were not elicited using standardized mania rating scale instruments.

Results: One case of mania occurred in the placebo group (0.1%), and two cases of hypomania were observed in the duloxetine-treated group (0.2%). Among hypomanic-like symptoms, only insomnia was significantly higher in the duloxetine group than in the placebo group ($p < 0.05$).

Conclusions: Duloxetine was associated with a low incidence of treatment-emergent hypomania, mania, or hypomanic-like symptoms in patients with major depressive disorder (MDD). The low incidence reported here may be due to greater diagnostic diligence on the part of the investigators. It is possible that the cases reported likely reflect inclusion of misdiagnosed bipolar II patients rather than true unipolar MDD cases. The effect of duloxetine in patients with bipolar depression is not known.

Keywords: Duloxetine; Major depressive disorder; Hypomania; Mania; Unipolar

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1. Introduction

Bipolar disorder is a common psychiatric illness that is often misdiagnosed or underdiagnosed (Akiskal et al., 2000; Hirschfeld, 2001; Benazzi and Akiskal, 2001) and the rate of manic switch during treatment of depression in bipolar patients reported in the literature ranges from 2.2% to 70% (Amsterdam et al., 1998; Angst, 1985; Benazzi, 1997; Ghaemi et al., 2000; Henry et al., 2001; Rabkin et al., 1985). Up to 50% of patients diagnosed with major depressive episodes may have bipolar type II disorder (Benazzi and Akiskal, 2003), thus making it possible for many so-called 'unipolar' patients to be diagnosed as bipolar II patients.

Treatment studies of major depression reveal low rates of treatment-emergent hypomania, with tricyclic antidepressants (TCAs) producing higher rates than selective serotonin reuptake inhibitors (SSRIs). Presumably this effect is due to the inclusion of bipolar patients in these studies of "unipolar major depression". Peet (1994) reported manic switching in 3.7% and 11.2% of bipolar patients receiving SSRIs and TCAs, respectively, and other studies have reported that TCAs promote switching in up to three times as many cases as SSRIs (Howland, 1996; Nielsen et al., 1993; Peet, 1994). Serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors (SNRIs) are similar to heterocyclic TCAs in their ability to block the reuptake of 5-HT and NE (Bymaster et al., 2001; Tatsumi et al., 1997). In major depressive disorder (MDD) trials with the SNRI venlafaxine, treatment-emergent mania or hypomania occurred in 0.5% of venlafaxine-treated patients compared with 0% of placebo-treated patients (Physician's Desk Reference, 2002).

Duloxetine hydrochloride, a selective 5-HT and NE reuptake inhibitor is relatively balanced in its affinity for both 5-HT and NE reuptake inhibition (Wong and Bymaster, 2002). Duloxetine has been shown to be safe and effective in the treatment of MDD (Detke et al., 2002a,b; Nemeroff et al., 2002). However, the risk of treatment-emergent mania or hypomania associated with duloxetine in patients diagnosed with major depression has not been evaluated. This report investigates the rate of treatment-emergent mania, hypomania, and hypomanic-like symptoms observed during clinical trials of patients with MDD who were treated with duloxetine.

2. Methods

This investigation included data from eight placebo-controlled, randomized, multi-center, double-blind clinical trials evaluating the efficacy of duloxetine in patients diagnosed with MDD. Ethics or institutional review boards at each study site approved the protocols, and all patients provided signed informed consent prior to study participation, in accordance with the Declaration of Helsinki.

All randomized patients from acute placebo-controlled trials of MDD were included in this assessment. All eight studies had identical inclusion and exclusion criteria. Male and female patients who were at least 18 years of age were included in these trials. All patients met diagnostic criteria for MDD defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The diagnosis was confirmed by the Mini International Neuropsychiatric Interview (MINI), a standardized diagnostic interview based on DSM-IV criteria (Sheehan et al., 1998). Patients were required to score ≥ 15 on the $HAMD_{17}$ and ≥ 4 on the CGI-S for at least two consecutive visits prior to randomization.

Patients were excluded if they had a lifetime history of bipolar disorder or any other primary Axis I disorder other than MDD. In addition, patients with an Axis II disorder that could interfere with protocol compliance, a history of substance abuse within the last year, a positive urine drug screen at study entry, a risk for suicide, a lack of response to two or more adequate courses of antidepressant therapy in the current episode, or a serious comorbid medical illness were also excluded. The MINI was utilized to diagnose patients with MDD and exclude patients with bipolar disorder. The period of active treatment for the studies ranged from 8 to 9 weeks depending on the design of the study, and the doses ranged from 40 to 120 mg of duloxetine. For this analysis, treatment-emergent manic- or hypomanic-like events were assessed over the entire treatment period of each study. Adverse events were collected from spontaneous patient reports as well as a non-probing inquiry by the investigator at each visit and recorded regardless of perceived causality. The adverse events data were reviewed for symptoms characteristic of mania or hypomania identified by DSM-IV and in the Young Mania Rating Scale (YMRS), and were coded using the Medical Dictionary for Regula-