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# Duloxetine 60 mg once-daily in the treatment of painful physical symptoms in patients with major depressive disorder☆

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**Abstract**

*Background*: While emotional symptoms such as depressed mood and loss of interest have traditionally been considered to constitute the core symptoms of major depressive disorder (MDD), the prevalence and importance of painful physical symptoms such as back pain, abdominal pain, and musculoskeletal pain is becoming increasingly appreciated. Antidepressants possessing dual serotonin/norepinephrine (5-HT/NE) reuptake inhibition may demonstrate greater efficacy in the alleviation of pain. The efficacy of duloxetine, a balanced and potent dual reuptake inhibitor of 5-HT and NE, was evaluated within a cohort of depressed patients with associated painful physical symptoms.

*Methods*: In this multicenter, double-blind, placebo-controlled study, patients meeting DSM-IV criteria for MDD were randomized to receive placebo ($N = 141$) or duloxetine 60 mg QD ($N = 141$). Patients were required to have a 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$) total score $\geqslant 15$, a Clinical Global Impression of Severity (CGI-S) score $\geqslant 4$, and a Brief Pain Inventory (BPI) Average Pain score $\geqslant 2$ at baseline. The primary efficacy measure was the BPI Average Pain score, while secondary measures included other BPI items, the $HAMD_{17}$ total score, CGI-S, the Patient Global Impression of Improvement (PGI-I) scale, Visual Analog Scales (VAS) for pain, and the Symptom Questionnaire, Somatic Subscale (SQSS). Safety was evaluated by recording treatment-emergent adverse events (spontaneously reported), vital signs, and laboratory analytes.

*Results*: Mean changes in BPI Average Pain for duloxetine- and placebo-treated patients differed significantly at most visits, but only approached significance at endpoint ($p = 0.066$). For the main effect of treatment (pooling all visits), significant advantages for duloxetine-treated patients were found in 10 of 11 assessed BPI pain severity and pain interference items, in addition to VAS overall pain and back pain. Mean changes in pain measures for duloxetine-treated patients corresponded to improvements of 25–50%, compared with 19–39% for placebo. Mean changes at endpoint in depression rating scales ($HAMD_{17}$, CGI-S, PGI-I) did not differ significantly between duloxetine and placebo treatment groups due to unusually high placebo response. The magnitude of placebo treatment effects (as measured by $HAMD_{17}$ total score and Maier subscale) was significantly smaller in patients with $\geqslant 1$ previous depressive episode, compared to those patients with no previous episodes. In patients with $\geqslant 1$ previous depressive episode the advantage of duloxetine over placebo was similar to previous studies. Rates of discontinuation due to adverse events were 14.2% vs. 2.1% for duloxetine and placebo, respectively ($p < 0.001$). Treatment-emergent adverse events reported at a significantly higher rate by duloxetine-treated patients included nausea, dry mouth, fatigue, and decreased appetite.

*Conclusions*: In this study, duloxetine (60 mg QD) was shown to be an effective treatment for the painful physical symptoms which are frequently associated with depression. Improvements in pain severity occurred independently of changes in depressive symptom severity.


*Keywords:* Duloxetine; Depression; Pain; Physical symptoms; Serotonin; Norepinephrine

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## 1. Introduction

Major depressive disorder (MDD) represents one of the most serious challenges faced by healthcare providers throughout the world, affecting some 18 million people in the United States and 340 million people globally (Greden, 2001). The negative impact of MDD upon patient well-being and functioning is comparable to that of major chronic medical conditions such as diabetes, hypertension, coronary artery disease, and arthritis (Wells et al., 1989). Given the enormous impact of depression upon both the individual patient and the healthcare system as a whole, the need for effective treatment is clear.

Antidepressant medications, in particular the selective serotonin reuptake inhibitors (SSRIs), currently represent the first line of treatment for MDD. Although SSRIs offer distinct advantages over tricyclic antidepressants (TCAs) in terms of improved patient safety and lower rates of treatment discontinuation (Anderson and Tomenson, 1995), meta-analyses comparing remission rates for the two classes of medications have failed to find an advantage for SSRIs (Anderson and Tomenson, 1994; Steffens et al., 1997).

The prospect of an advance in the pharmacologic treatment of depression was provided by studies that focused upon achieving selective reuptake inhibition of both serotonin (5-HT) and norepinephrine (NE). It was demonstrated that a dual reuptake inhibitor (clomipramine) provided efficacy superior to that of an SSRI comparator (Citalopram, 1986; Paroxetine, 1990), and that a combination of selective 5-HT (fluoxetine) and NE (desipramine) inhibitors provided efficacy superior to that of desipramine alone (Nelson et al., 1991). Furthermore, an analysis of pooled efficacy data for venlafaxine, which inhibits the reuptake of 5-HT and NE at higher doses, revealed higher rates of remission than those observed with SSRIs or placebo (Thase et al., 2001).

Depression is a multifaceted disease, encompassing a spectrum of both emotional (e.g. depressed mood, guilt, anxiety) and physical symptoms (sleep disruption, gastrointestinal disturbance, loss of appetite, fatigue, unexplained aches and pains) (Rakel, 1999). Patients with MDD frequently present with physical, rather than emotional, symptoms especially in the primary care setting (Kroenke et al., 1994; Simon et al., 1999). Physical symptoms add to the functional impairment of the patient, increase health care utilization (Shaw and Creed, 1991), and may also hinder the diagnosis of MDD. The level of recognition of depressive illness decreases appreciably when presentations involve primarily physical complaints (Gerber et al., 1989; Posse and Hallstrom, 1998).

Within the domain of physical symptoms associated with depression, those involving pain (e.g. headache, neck and back pain, abdominal pain, diffuse musculoskeletal pain) are particularly common (Stahl, 2002; Fava, 2002). In a recent study, the prevalence of chronic painful physical conditions (CPPCs) was assessed in almost 19,000 respondents to a telephone survey. Those subjects diagnosed with MDD had a prevalence of CPPCs four times that of non-depressed subjects (odds ratio 4.0; 95% CI 3.5–4.7), while the presence of a CPPC was an independent contributor to the presence of MDD with an odds ratio of 3.6 (Ohayon and Schatzberg, 2003).

Since pain often has an adverse effect upon other depressive symptoms (for example, it may induce or exacerbate low energy, sleep disturbance, and anxiety (Von Korff and Simon, 1996)), it may influence the manifestation and course of depressive illness, and in turn play a role in treatment outcomes. In a study of 573 depressed patients receiving SSRI treatment, the odds ratio for poor depression treatment response at three months was 1.5 for patients with mild pain, 2.0 for moderate pain, and 4.1 for those with severe pain (Bair et al., 2004). The intimate relationship between pain and depression, and the growing evidence of a connection between treatment outcomes in these conditions, suggests that maximal patient benefit may result from treatments which effectively address both emotional and physical symptom domains.

In addition to their key role in the neurobiology of depressive illness, a considerable body of evidence suggests that 5-HT and NE modulate spinal nociceptive transmission within descending pain pathways (Jones, 1991; Fields et al., 1991). Antidepressant medications, in particular the TCAs, are frequently prescribed for the treatment of painful conditions such as fibromyalgia, migraine headaches, and diabetic neuropathy (Salerno et al., 2002; McQuay et al., 1996). Analysis of efficacy data from these studies has suggested that, for some painful conditions, TCAs are more likely to show a beneficial outcome than SSRIs (O'Malley et al., 1999; Lynch, 2001; Goodnick, 2001). Since many TCAs (for example, amitriptyline) inhibit the reuptake of both 5-HT and NE, it has been suggested that medications achieving dual 5-HT/NE reuptake inhibition may exhibit superior analgesic efficacy compared to those which influence a single neurotransmitter (Fishbain et al., 2000; Collins et al., 2000).

The antidepressant duloxetine is a balanced and potent dual reuptake inhibitor of 5-HT and NE (Bymaster et al., 2001). Previous studies have established the safety and efficacy of duloxetine in the treatment of MDD (Nemeroff et al., 2002; Detke et al., 2002a,b; Goldstein et al., 2002). In two of these studies a once-daily 60 mg duloxetine dose was also shown to produce significant improvement in a number of painful physical symptoms associated with MDD (Detke et al., 2002a,b). In these initial investigations, however, patients were not selected on the basis of their pre-treatment levels of pain.