

Resolution of Sleepiness and Fatigue in Major Depressive Disorder: A Comparison of Bupropion and the Selective Serotonin Reuptake Inhibitors

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Background: The purpose of this study was to examine whether the treatment of major depressive disorder (MDD) with the norepinephrine-dopamine reuptake inhibitor (NDRI) bupropion results in a greater resolution of sleepiness and fatigue than with the selective serotonin reuptake inhibitors (SSRIs).

Methods: Six double-blind, randomized clinical trials comparing bupropion ($n = 662$) with an SSRI ($n = 655$) for the treatment of MDD were pooled. Hypersomnia scores were defined as the sum of scores of the Hamilton Depression Rating Scale (HDRS) items #22, 23, and 24. Fatigue scores were defined as the score of HDRS item #13.

Results: There was a greater improvement in hypersomnia scores among bupropion-treated than SSRI-treated ($p < .0001$) or placebo-treated patients ($p = .0008$). There was also a greater improvement in fatigue scores among bupropion-treated ($p < .0001$) and SSRI-treated ($p = .0005$) than placebo-treated patients as well as a greater improvement in fatigue scores among bupropion-treated than SSRI-treated patients ($p = .0078$). Fewer bupropion-remitters than SSRI-remitters experienced residual hypersomnia (20.5% vs. 32.1%; $p = .0014$) or residual fatigue (19.5% vs. 30.2%; $p = .0020$).

Conclusion: Treatment of MDD with the NDRI bupropion resulted in a greater resolution of sleepiness and fatigue than SSRIs treatment. Although preliminary, these results warrant prospectively designed studies examining potential differences between bupropion and the SSRIs on these specific depressive symptoms.

Key Words: Sleepiness, fatigue, bupropion, SSRIs, MDD, treatment

It has been estimated that as many as one-half of all patients with major depressive disorder (MDD) do not experience sufficient symptom improvement despite several adequate trials of antidepressant drugs (Fava and Davidson 1996; Petersen et al 2005), with most patients taking a selective serotonin reuptake inhibitor (SSRI) as their initial treatment (Petersen et al 2002). To make matters worse, among those who remit, residual symptoms are common (Nierenberg et al 1999) and are associated with impaired psychosocial functioning (Papakostas et al 2004; Simon et al 2000) and increased relapse rates (Paykel et al 1995). Until recently, known differences among antidepressant drugs were generally limited to aspects of safety and tolerability (Papakostas and Fava 2005). However, over the past few years, a number of studies have emerged suggesting that there might be differences among antidepressant classes in their ability to resolve specific symptoms of depression (Fava et al, unpublished data, 2005; Goldstein et al 2004; Winokur et al 2005).

Fatigue is among the most common symptoms of MDD, present in anywhere from 73% to 97% of outpatients (Baker et al 1971; Maurice-Tison et al 1998; Tylee et al 1999). In fact, in a large Pan-European survey of adults who had experienced depression within the past 6 months, almost as many patients complained of fatigue (73%) as low mood (79%) (Tylee et al 1999). In addition, fatigue was reported as the second-most common residual depressive symptom among fluoxetine-remitters

in one study (Nierenberg et al 1999). The presence of fatigue has also been identified as a risk factor predictive of a chronic course for depressive illness (Moos and Cronkite 1999). Although hypersomnia, or excessive sleepiness, is not as common as fatigue in MDD, it has been reported to be present in approximately one in six MDD outpatients (Horwath et al 1992; Posternak and Zimmerman 2001) and in as many as one in three outpatients with atypical MDD (Posternak and Zimmerman 2001). Interestingly enough, as many as 70% (21 of 30) of MDD patients who presented with hypersomnia in one study continued to complain of hypersomnia after remission of symptoms during treatment with fluoxetine (Worthington et al 1995). Unfortunately, however, even though both fatigue and hypersomnia feature prominently as residual symptoms of depression (Fava 2003, 2004), to date, there is a paucity of studies addressing the relative efficacy of antidepressant drugs in resolving fatigue and sleepiness in MDD (Demyttenaere et al 2005).

Bupropion hydrochloride, available in the United States for the treatment of depression since 1989 (Fava et al 2005), is a norepinephrine and dopamine reuptake inhibitor (NDRI) with no clinically significant affinity for the serotonergic transporter or the serotonergic, cholinergic, adrenergic, or histaminergic receptors (Ascher et al 1995). To date, published studies suggest that bupropion is as effective as the SSRIs in the overall treatment of MDD (Thase et al 2005), as effective as the SSRIs in the treatment of anxious symptoms of depression (Trivedi et al 2001), and as effective as the SSRIs in the overall treatment of depression regardless of the degree of anxiety at baseline (Rush et al 2001a, 2001b). However, it is unclear whether the treatment of MDD with bupropion results in greater resolution of particular symptoms of depression than the SSRI. Although the biological bases of excessive sleepiness and fatigue in patients with MDD have not been fully elucidated, a number of studies suggest that the neurotransmitters dopamine and norepinephrine play a key role in the pathophysiology of these symptoms (Stahl et al 2003). Therefore, the purpose of the present work was to examine whether the treatment of MDD with the NDRI bupropion results in a greater resolution of sleepiness and fatigue than the SSRIs.

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Methods and Materials

The present work involved pooling individual patient data from six double-blind, randomized clinical trials sponsored by GlaxoSmithKline (Research Triangle Park, North Carolina) comparing bupropion with an SSRI for the treatment of MDD that also included outcome measures for both hypersomnia and fatigue. Although to date (October 2005) a total of 10 studies sponsored by GlaxoSmithKline comparing bupropion with an SSRI for the treatment of MDD have been conducted, 4 of these studies were excluded from the pooled analysis because they did not include Hamilton Depression Rating Scale (HDRS- Hamilton 1960) versions which also measure hypersomnia (i.e., 17- or 21- rather than 24-, 28- or 31-item versions of the HDRS were used in those trials). Among the six studies pooled, three used sertraline, one used paroxetine, and two used escitalopram as the SSRI comparator (see Table 1). To our knowledge, studies comparing bupropion with the SSRIs for MDD sponsored by sources other than GlaxoSmithKline have not been conducted. Therefore, to the best of our knowledge, the present analysis is all-inclusive.

All six studies included in the present analysis were conducted in accordance with guidelines set by the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (2005), including the administration of institutional review board-approved written informed consent. All patients met criteria for MDD as defined in DSM-IV, and all studies included a 1-week screening phase preceding the double-blind phase. Characteristics of these trials are listed in Table 1.

Definitions and Efficacy Assessments

An intent-to-treat (ITT) analysis of all patients randomized to treatment with the last available observation carried forward (LOCF) was applied in the present analyses. Clinical response was defined as a 50% or greater decrease from baseline to end point in 17-item HDRS (HDRS-17) total score. Remission was defined as an HDRS-17 total score ≤ 7 at end point. Hypersomnia score was defined as the sum of scores of HDRS items #22 (going to bed early), 23 (oversleeping in AM), and 24 (daytime napping). Fatigue score was defined as the score of HDRS item #13. Improvement of a symptom (hypersomnia, fatigue) was defined as the change in scores for that symptom from baseline to end point. Resolution of a symptom was defined as an end point score of 0, whereas residual symptomatology was defined as an end point score > 0 . To reduce the likelihood of chance findings, these definitions were strictly agreed upon by the principal author and the principal biostatistician of the manuscript a priori.

Statistical Tests

To compare the degree of improvement of hypersomnia and fatigue symptoms between bupropion-, SSRI-, and placebo-treated groups, Cochran-Mantel-Haenszel (CMH) row-mean-score tests for the change in each symptom (hypersomnia, fatigue), controlling for baseline level of severity of that symptom, were conducted. Similarly, CMH row-mean-score tests for the severity of each symptom at end point (hypersomnia, fatigue scores) among treatment-remitters were conducted to compare

Table 1. Studies Pooled and Excluded

Trial	n	Baseline Severity for Inclusion	Treatments	Dose mg (mean) Forced Titration	Duration (weeks)
Included Studies					
Kavoussi et al 1997	248	HDRS21 > 17	Bupropion SR	100–300 (224)	16
			Sertraline	50–200 (104)	
Croft et al 1999	360	HDRS21 > 17	Bupropion SR	150–400 (293)	8
			Sertraline	50–200 (121)	
			Placebo		
Coleman et al 1999	364	HDRS21 > 17	Bupropion SR	150–400 (290)	8
			Sertraline	50–200 (107)	
			Placebo		
Weihs et al 2000	100	HDRS21 > 17	Bupropion SR	100–300 (199)	6
			Paroxetine	10–40 (22)	
Clayton et al 2006	368	HDRS17 > 18	Bupropion XL	300–450 (308)	8
			Escitalopram	10–20 (13)	
			Placebo		
Clayton et al 2006	397	HDRS17 > 18	Bupropion XL	300–450 (322)	8
			Escitalopram	10–20 (13)	
			Placebo		
Excluded Studies					
Feighner et al 1991	123	HDRS21 > 19	Bupropion	225–450 (338)	6
			Fluoxetine	20–80 (26)	
Unpublished ^a	467	HDRS21 > 19	Bupropion SR	150–400 (282)	8
			Fluoxetine	20–60 (28)	
			Placebo		
Coleman et al 2001	456	HDRS21 > 19	Bupropion SR	150–400 (289)	8
			Fluoxetine	20–60 (30)	
			Placebo		
Kennedy et al 2006	140		Bupropion SR	150–300	8
			Paroxetine	20–40	

^aData on file. GlaxoSmithKline, Research Triangle Park, North Carolina.

HDRS, Hamilton Depression Rating Scale; SR, sustained release; XL, extended release.

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