Functional Status in Depressed Patients: The Relationship to Disease Severity and Disease Resolution

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Background: We set out to measure the impact of depression and its clinical resolution on patients' functional status.

Method: The Work and Social Disability Scale (WSDS), a five-category investigator-rated scale measuring patient functional status, was completed at baseline and study discontinuation in a 56-day, open, uncontrolled study evaluating the safety of a sustained release (SR) formulation of bupropion in 3167 patients at 105 sites. To be included in the study, patients had to be 18 years or older, have a diagnosis of depression, and be considered appropriate for treatment with bupropion SR. The proportion of patients in each WSDS category, for those patients taking more than 7 days of bupropion SR (N = 2915), was assessed at screen and study discontinuation. The percentage of patients with improved WSDS scores at 56 days was also measured for all patients and correlated with patient and treatment characteristics.

Results: Of the patients entering the trial, 61.8% were markedly or severely impaired in their work or social activities, and only 5.4% were mildly or not impaired. At study discontinuation, more than 54% of patients were judged by the investigator to have very much or much improvement in their clinical symptoms. Results on the WSDS correlated with the clinical improvements; only 22.3% were markedly or severely impaired; and 50.0% were mildly or not impaired at study discontinuation. In addition, 63.9% of patients had less work or social disability at the end of the trial than at study entry. Functional status improved more in patients who had not previously been treated for the episode, had more severe depression at study entry, and had a higher dose and duration of treatment with bupropion SR.

Conclusion: The results show that depression results in significant impairment in patients' functional status. Functional status improved in patients treated with bupropion SR for up to 56 days. This improvement was highly correlated with improvement in clinical symptoms and was related to patient characteristics at study entry as well as to treatment patterns during the study.

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Major depressive disorder results in a substantial burden on society in terms of its impact on the patient and its economic costs. The economic costs are due to the medical care use and reduced productivity associated with depression. A recent study by Greenberg et al.[1] of the economic burden of depression in the United States estimated the total burden per year for 1990 to be $43.7 billion, of which $12.4 billion (28%) were medical care costs, $7.5 billion (17%) were mortality costs (because of lost earnings after suicide), and $23.8 billion (55%) were attributable to lost productivity. The productivity costs were distributed between lost days of work and days at work with reduced productivity; the latter accounted for $12 billion of the estimated lost productivity costs.

The costs associated with reduced productivity while at work in the Greenberg et al. study[1] were estimated by assuming a 20% reduction in productivity. The assumed value was based on studies of the average reductions in earnings due to the presence of any mental disorder estimated by Bartel and Taubman[2] and Frank and Gertler.[3] Very few studies have directly measured the impact of depression and its treatment on patient well-being and functioning, which includes work productivity, even though this aspect of the disease accounts for approximately 55% of its economic impact. One exception is the Mintz et al. study,[4] which evaluated the effects of antidepressants and psychotherapy on work impairment in depressed patients by using data from 10 published studies. The authors demonstrated that work improvement was correlated with symptomatic improvement although work recovery generally took longer. They also demonstrated that affective work impairment (subjective emotional states at work such as distress, feelings of shame, or lack of interest) was associated with mild depression, while functional impairment (observable behaviors such as absenteeism, performance adequacy, and interpersonal conflict) was associated with more severe disease.

Clinical studies of new treatments for depression have demonstrated improvements in symptom outcomes, measured by using scales such as the Hamilton Rating Scale for Depression (HAM-D)[5] and Clinical Global Impressions.[6] However, these studies have generally not attempted to measure improvements in patient functioning and work productivity. Since work disability is such an important component of the economic impact of the disease, measurement of the effect of new treatments on work function is important.

In a recent study of the safety of up to 56 days of treatment of depressed patients with a sustained release (SR) formulation of bupropion in an uncontrolled trial of more than 3000 patients, a measure of patient work and social functional status was included. Because of the large size of the trial, a simple measure—one that could readily be completed by the investigator in consultation with the patient—was desirable. The Work and Social Disability Scale (WSDS) was chosen.[7,8] The reasons for the inclusion of the WSDS in this trial were to generate empirical information about the impact of depression and its clinical resolution on patient functional status and to examine the correlates/determinants of functional impairment in depression and its resolution with treatment. The results of the analysis of the WSDS are presented in this paper.

METHOD

Clinical Trial Design

The clinical trial was a 56-day open, uncontrolled, multicenter study evaluating the safety of bupropion SR. A total of 3167 patients were evaluated at 105 sites. The study was divided into three phases: a screening phase, a treatment phase, and a continuation phase. At the screening phase, the investigator determined whether the patient satisfied the inclusion and exclusion criteria, obtained informed consent, and completed the WSDS to measure functional status, a psychiatric history, and the Clinical Global Impressions-Severity of Illness (CGI-S) scale to measure severity of the clinical symptoms of depression.

To be included in the study, the patient had to be 18 years or older with a diagnosis of depression for which antidepressant treatment was clinically indicated and had to be considered appropriate for treatment with bupropion SR. Previous treatment with bupropion, a history of eating disorders, a predisposition to seizures, unstable medical disorders, pregnancy, and recent use of any neuroleptic or antidepressant excluded patients from the study. Patients who were actively suicidal or who refused to give informed consent were also excluded.

The treatment phase consisted of 56 days of treatment with bupropion SR. Dosing was initiated at 50 mg twice a day and escalated to 100 mg twice a day at Day 5 and 150 mg twice a day at Day 8. If patients could not tolerate the higher doses, the investigator was allowed to reduce the treatment to a lower dose. Patients returned for treatment visits on Days 14, 28, and 56, or more frequently if indicated. At Day 56, or earlier if the patient prematurely discontinued from the trial, the physician completed the WSDS to measure patient functional status, the CGI-S to measure severity of the clinical symptoms of depression, and the Clinical Global Impressions-Improvement (CGI-I) scale to measure the degree to which the clinical symptoms abated. After Day 56, continued treatment with bupropion SR was allowed if the patient wished and at the discretion of the investigator; 1577 patients chose to continue treatment after Day 56.

Table 1. Work and Social Disability Scale

Score	Severity of Disability	Definition
1	Absent	No complaints and normal activity
2	Mild	Symptoms complained of by patient but not interfering with normal work or social activities
3	Moderate	Symptoms interfering with normal work or social activities in minor ways
4	Marked	Normal work or social activities interfered with markedly, but not prevented or radically changed
5	Severe	Normal work or social activities either radically changed or prevented

Work and Social Disability Scale

The WSDS has previously been used to assess the efficacy of benzodiazepines and antidepressants in treating agoraphobia[9,10] and in a retrospective study of behavioral therapy in phobic patients.[8] The scale, presented in Table 1, is an investigator-rated scale that assesses disability in social and working activities. Higher scores represent states associated with greater disability, whereas lower scores represent less disability.

Statistical Analyses

In past studies using the WSDS, investigators have computed the percentage of patients with different levels of improvement in functional status. In these studies, patients are defined as improved if their WSDS score decreased by one or more points and markedly improved if their WSDS score decreased by two or more points.[8,10] Results from this study are presented that use these outcome measures as well as the frequency distribution of patients at each level of disability at screen and end of study or premature discontinuation. Hereafter, the phrase *study discontinuation* will be used to refer to the end of the study at Day 56 for patients completing the treatment phase and to the time when patients prematurely discontinue for those who did not complete the treatment phase.

The patient population studied consisted of those who had received at least 7 days of bupropion SR therapy (2915 patients). To determine whether clinical, treatment, or demographic variables impact the magnitude of change

Table 2. Characteristics of Patients (N = 2915) Who Had > 7 Days of Bupropion SR Treatment*

Population Subgroup	N	%
Gender		
Men	1106	37.9
Women	1809	62.1
Compliance > 80%		
Yes	2778	95.3
No	137	4.7
Completed at least 56 days on study medication		
Yes	2060	70.7
No	855	29.3
Previous use of antidepressant therapy for this episode		
Yes	1124	38.6
No	1791	61.4
Mean daily dose of bupropion SR		
< 150 mg/d	196	6.7
150–250 mg/d	934	32.1
> 250 mg/d	1785	61.2
CGI-S score at study entry		
Mild (scores = 1–3)	310	10.6
Moderate (score = 4)	1728	59.3
Severe (scores = 5–7)	877	30.1
CGI-I score at study discontinuation		
Very much improved	663	22.8
Much improved	934	32.0
Minimally improved	612	21.0
No change	458	15.7
Minimally worse	139	4.8
Much or very much worse	42	1.4
Assessment missing	67	2.3

*Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale; CGI-S = Clinical Global Impressions-Severity of Illness scale (range, 1–7).

in the WSDS seen over the trial period, the percentage of patients with improved functional status are presented for the total trial population, as well as for subpopulations stratified by gender, previous use of antidepressant for this episode, CGI-S at study entry, whether the patient completed the trial, mean dose of bupropion SR, compliance status, and CGI-I score at study discontinuation. Both descriptive and logistic regression analyses were performed. Pearson correlation coefficients were estimated to determine the correlation between the CGI-I score and the improvement in the WSDS score and the correlation between CGI-S scores and WSDS at both screen and study discontinuation and between the changes in these two variables between screen and study discontinuation.

RESULTS

Sample Composition

The composition of the study sample consisted of 2915 patients who completed 7 days of therapy. These patients did not differ from all study patients by sex, pervious use of antidepressants, or severity of illness at baseline. Of these patients, 2848 (97.7%) completed WSDS at both baseline and study discontinuation. Thus, most of the 29% of patients who did not complete 56 days of treatment still completed WSDS at study discontinuation. Table 2 presents the clinical and demographic variables used in the analysis. As expected for a study of depression, there were more women (62.1%) than men in the study. Altogether, 70.7% of patients completed the 56-day treatment phase of the study. In addition, 38.6% of patients had received previous antidepressant treatment for the current depressive episode. While the target dose for the study was 300 mg/day, 38.7% had a mean daily dose level of 250 mg or below. The majority of patients (95.3%) were compliant with their dosing regimen. Almost 90% of patients were moderately or severely depressed when they entered the study, as assessed by the CGI-S scale, and about 54% were very much or much improved at the time of study discontinuation, as assessed by the CGI-I scale.

Table 3. Work and Social Disability Scale (WSDS) Score at Screen and Study Discontinuation in Study Population (N = 2915)

Disability Level, WSDS score	Screen		Discontinuation	
	N	%	N	%
Absent, 1	10	0.4	611	21.0
Mild, 2	148	5.1	846	29.0
Moderate, 3	954	32.7	740	25.4
Marked, 4	1432	49.1	482	16.6
Severe, 5	371	12.7	169	5.8
Assessment missing	0	0	67	2.3

Work and Social Disability

Work and social disability was found to be significantly affected by depression and its clinical resolution during treatment. Table 3 presents the screen and study discontinuation scores for the population analyzed. At screen, 61.8% of the patients were markedly (WSDS score = 4) or severely (WSDS score = 5) impaired in their work or social activities and only 5.4% were not impaired (WSDS score = 1) or only mildly so (WSDS score = 2). At study discontinuation only 22.3% were markedly or severely impaired while 50.0% were not impaired or only mildly so. The correlation between CGI-S and WSDS at screen was R = .563 (p = .0001) and at study discontinuation the correlation between the CGI-S and WSDS was higher, R = .874 (p = .0001). The correlation between the change in CGI-S score and change in WSDS score from screen to study discontinuation was R = .829 (p = .0001). When the screen and discontinuation WSDS scores were computed by severity of illness at study entry, it showed that the more severely ill patients were more functionally impaired at study entry than the less severely ill, and fewer of the more severely ill patients were able to function normally at the end of the study (see Table 4).

Of those who chose to continue taking bupropion SR after the end of the 56-day treatment phase (1577 patients), 71.6% were not functionally impaired or only

Table 4. Functional Ability at Screen and Study Discontinuation by Severity of Illness in Study Population (N = 2915)

CGI-S Score at Screen[a]	WSDS Score of 1 or 2 at Screen		WSDS Score of 1 or 2 at Study Discontinuation	
	N	%	N	%
Mild (N = 310)	88	28.4	197	63.6
Moderate (N = 1728)	67	3.9	906	52.4
Severe (N = 877)	3	0.3	354	40.4

[a]Mild = CGI-S scores 1–3, Moderate = CGI-S score 4, and Severe = CGI-S scores 5–7.

Table 5. Change in Scores on WSDS in Trial Population (N = 2915) Between Baseline and Study Discontinuation*

WSDS Score Change	Improved		Worsened	
	N	%	N	%
1 point	791	27.1	124	4.3
2 points	703	24.1	53	1.8
3 points	308	10.6	26	0.9
4 points	61	2.1	1	0.0
Total	1863	63.9	204	7.0

*The scores for 848 patients (29.1%) were unchanged (781) or missing (67).

Table 6. Change in WSDS Score by Population Characteristics

Population Subgroup	Number of Patients	Improved[a] (%)	Markedly Improved[b] (%)
Gender			
Men	1106	64.0	36.3
Women	1809	63.9	37.1
Compliance > 80%			
Yes	2778	62.8	36.1
No	137	31.3	13.5
Completed at least 56 days on study medication			
Yes	2060	80.6	48.7
No	855	23.6	8.1
Previous use of antidepressant therapy for this episode			
Yes	1124	55.8	30.2
No	1791	69.0	40.9
Mean daily dose of bupropion SR			
< 150 mg/d	196	37.2	14.8
150–250 mg/d	934	49.7	26.8
> 250 mg/d	1785	74.3	44.4
CGI-S score at study entry			
Mild (scores = 1–3)	310	52.3	21.9
Moderate (score = 4)	1728	64.4	35.9
Severe (scores = 5–7)	877	67.1	43.8
CGI-I score at study discontinuation			
Very much improved	663	98.5	84.8
Much improved	934	91.1	48.1
Minimally improved	612	51.8	9.2
No change	458	7.2	0.7
Minimally worse	139	5.8	1.4
Much or very much worse	42	0.0	0.0
Assessment missing	67	…	…

[a]WSDS score decreased by ≥ 1.
[b]WSDS score decreased by ≥ 2.

Table 7. Logistic Regression Analyses for Change in WSDS Scores

Independent Variable	Improvement in WSDS[a]		Marked Improvement in WSDS[b]	
	Parameter Value	p Value	Parameter Value	p Value
Intercept	0.0575	.9241	–1.4551	.0164
Sex (M = 1, F = 2)	0.1198	.2126	0.0941	.2819
Compliance > 80% (Yes = 1, No = 2)	0.3790	.1143	0.1614	.5407
Completed 56 days of treatment (Yes = 1, No = 2)	–2.5888	.0001	–2.3457	.0001
Taken previous medication (Yes = 1, No = 2)	0.6573	.0001	0.4353	.0001
Mean dose of bupropion SR (mg/d)	0.0034	.0039	0.0031	.0081
Baseline CGI-S score (range, 1–7)	0.3548	.0001	0.4548	.0001

[a]WSDS score decreased by one or more points.
[b]WSDS score decreased by two or more points.

mildly so at 56 days, and 32.2% of those had no impairment. After further treatment, their functional status continued to improve and at 112 days, 72.3% were not impaired or only mildly so, while 43.5% of those had no impairment. The increase in the percentage with no impairment from 32.2% to 43.5% indicates a continuing improvement in functional status after Day 56.

Table 5 presents the data on the percentage of patients whose work and social functional status improved, was unchanged, or deteriorated by one or more points from study entry until discontinuation. This table shows that 63.9% of patients had improved functional status by the end of the 56-day treatment phase as measured by a decrease of one or more points on the WSDS.

Table 6 presents the outcome measures, improvement (defined by a reduction in WSDS score of one or more points) and marked improvement (defined by a reduction in WSDS score of two or more points), for each of the population subgroups. There were no differences in improvement rates by gender. However, a higher compliance rate and a higher mean daily dose of bupropion SR were both associated with higher improvement rates. There was a positive association between the WSDS improvement and completing the 56-day treatment phase. Those who had previous use of an antidepressant for the episode were less likely to show improvement in WSDS scores. The more severely ill at study entry were more likely to improve with treatment, and there was a strong relationship between the CGI-I scores and WSDS improvement rates. The correlation coefficient between the CGI-I score and the WSDS improvement rates was R = .81 (p = .0001). The high correlation coefficient demonstrates that clinical improvement in treated depressive disorder is accompanied by improvement in patient functional status.

Table 7 presents the results of the logistic regression analyses. The probability of improvement or marked improvement in functional status is statistically significantly correlated with completing the study, not having been previously treated for the current episode of depression, a higher dose of bupropion SR, and a greater severity of clinical depression at study entry. The only difference between the regression and descriptive results was the impact of compliance rates with the trial drug regimen of over 80%, which was positively associated with WSDS improvement in the descriptive analysis but negatively associated in the regression analysis. However, the negative association was not statistically significant.

DISCUSSION

The results indicate that people with depression suffer from serious functional impairment as measured by the WSDS, and those with more severe depression have more functional impairment. Clinical resolution of the episode during treatment is associated with improvement in patients' functional status. Improvement in WSDS scores are highly correlated with the CGI rates of improvement scores as well as with the change in CGI severity of clinical depression scores.

There are several limitations of this study that must be considered when interpreting the results. First, the baseline measures are not necessarily reflective of the functional limitations of all depressed patients since they measure just those who were entered into the clinical trial. However, the correlation of illness severity at study entry with the WSDS scores allows for the results of the study to be generalized to populations with different levels of illness severity. A second limitation is the open design of the study that could result in bias in the investigators' assessment of improvement in functional status. A third limitation is the lack of a control group, which means that the improvements in clinical and functional status for patients treated with bupropion SR cannot be compared with an untreated or placebo group. In addition, apparent improvements in functional status due to regression to the mean of the trial patients cannot be separated from true improvements in functional status during the trial period. A fourth limitation is the possibility that baseline measurements may overstate the level of functional impairment because of cognitive disturbances in depressed patients.

The positive correlation of mean daily dose of bupropion SR with functional outcomes suggests that bupropion SR may be one cause of the clinical improvement and its associated improvement in functional status. But in this uncontrolled study, treatment impacts on clinical and functional status during the trial period cannot be separated from the impacts of regression to the mean, overstatement of baseline impairment, a placebo effect, and/or natural disease resolution and investigator bias.

Measures of the indirect costs of depression in terms of dollars and descriptive measures such as the WSDS have been neglected in the literature. In this study, there was a very high correlation between the clinician-rated improvements in clinical symptoms and clinician-rated improvements in functional status, demonstrating that such measurements can provide useful information about the impact of depression and its clinical resolution during treatment on patient functional status. Both clinician and patient self-reported measures of work loss and reduced productivity at work during randomized controlled trials of new antidepressants are needed to provide definitive measures of the impact of these drugs on the indirect costs of depression and should be part of such trials in the future.

The results of our analyses demonstrate that depression of sufficient severity for a patient to be enrolled in the clinical trial has a large negative impact on functional status and that this functional status is greatly improved as the clinical symptoms resolve. The changes in the WSDS scores indicate that significant social costs can be avoided by resolution of the symptoms of depression. Benefits from disease resolution will not only be experienced by patients but by their families, friends, and employers.

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