Bupropion Sustained Release for Bereavement: Results of an Open Trial

Sidney Zisook, M.D.; Stephen R. Shuchter, M.D.; Paola Pedrelli, B.A.; Jeremy Sable, M.D.; and Simona C. Deaciuc, M.D.

Objective: The present study was conducted to assess whether DSM-IV–defined bereavement responds to bupropion sustained release (SR).

Method: Twenty-two subjects who had lost their spouses within the previous 6 to 8 weeks and who met DSM-IV symptomatic/functional criteria for a major depressive episode were evaluated. Subjects completed the Hamilton Rating Scale for Depression (HAM-D), the Clinical Global Impressions scale, the Texas Revised Inventory of Grief, and the Inventory of Complicated Grief at baseline and follow-up. Subjects were treated with bupropion SR, 150 to 300 mg/day, for 8 weeks.

Results: Improvement was noted in both depression and grief intensity. For the intent-to-treat group, 59% experienced a reduction of ≥ 50% on HAM-D scores. The correlations between changes in the HAM-D scores and the grief scale scores were high, ranging from 0.61 ($p = .006$) to 0.44 ($p = .054$).

Conclusion: Major depressive symptoms occurring shortly after the loss of a loved one (i.e., bereavement) appear to respond to bupropion SR. Treatment of these symptoms does not intensify grief; rather, improvement in depression is associated with decreases in grief intensity. The results of this study challenge prevailing clinical wisdom that DSM-IV–defined bereavement should not be treated. Larger, placebo-controlled studies are indicated.

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Reprint requests to: Sidney Zisook, M.D., Department of Psychiatry, University of California San Diego, 9500 Gilman Dr., La Jolla, CA 92093 (e-mail: szisook@ucsd.edu).

The absence of published studies on the treatment of DSM-IV–defined bereavement or its DSM-III and -III-R predecessor, uncomplicated bereavement, is of little surprise. After all, these are defined as nonillnesses (V codes) that should, by definition, be relatively benign and short-lived. Yet some data suggest that major depressive symptoms occurring within the first 2 months of the death of a loved one (i.e., bereavement) may be associated with substantial suffering and role impairment,[1] be as chronic as non–bereavement-related major depressive episodes,[2] and even have psychobiological underpinnings seen in other major depressive cohorts.[3] The present study is meant to take a preliminary look at whether DSM-IV–defined bereavement responds to the antidepressant medication bupropion sustained release (SR) and whether large, controlled trials in this population are warranted.

METHOD

Potential subjects were identified by searching death certificate records from the Department of Vital Records in San Diego County, Calif. Over the 10-month enrollment period (Sept. 1998–July 1999), letters were sent to all 3998 surviving spouses within a 50-mile radius of the University of California, San Diego, 4 to 6 weeks after their spouse's death. The letter described the study and asked potential participants to call the research office if they felt they met criteria and were interested. Of the 85 widows/widowers who called and were prescreened by a research assistant, 30 were given appointments for intake interviews with the research assistant (P.P.) and principal investigator (S.Z.). Of those surviving spouses, 1 decided against participating, 7 did not meet all criteria, and 22 were enrolled.

Inclusion criteria were (1) death of a spouse within 2 months of the intake interview; (2) meeting symptomatic and functional criteria for a major depressive episode according to DSM-IV; (3) onset of present episode after death of spouse; (4) no preexisting dysthymic disorder immediately preceding the spouse's death; (5) stable medical health; (6) ability to attend weekly evaluations at the San Diego Veterans Affairs Medical Center; (7) not psychotic, suicidal, or abusing substances; (8) no history of mania; (9) no previous use of bupropion SR; and (10)

Table 1. Depression and Grief Scale Scores[a]

Measure	Completer Sample (N = 14)			Intent-to-Treat Sample (N = 22)		
	Baseline	Week 8	p Value	Baseline	Week 8 or Last Visit	p Value
Depression scores						
HAM-D						
Mean (SD) score	16.51 (4.15)	4.50 (3.28)	< .001	16.77 (3.36)	7.73 (5.69)	< .001
Mean improvement, %	...	73		...	54	
Patients with ≥ 50% improvement, %	...	86		...	59	
CGI-S						
Mean (SD) score	3.29 (0.73)	1.57 (0.65)	< .001	3.32 (0.85)	2.09 (1.06)	< .001
Mean improvement, %	...	52		...	37	
Patients with ≥ 50% improvement, %	...	64		...	45	
CGI-I						
Mean (SD) score	...	1.79 (0.80)	< .001	...	2.36 (1.22)	...
Patients with a score of 1 or 2, %	...	79		...	55	
Grief scores						
TRIG present mean (SD) score	54.43 (7.01)	49.71 (6.54)	.059	53.32 (7.60)	50.58 (6.04)	< .05
ICG mean (SD) total score	40.07 (13.95)	31.21 (9.59)	< .011	37.89 (12.53)	30.95 (8.64)	< .001
Depression/grief correlation, r value						
HAM-D/TRIG		0.51	.063		0.61	.006
HAM-D/ICG		0.21	> .10		0.44	.054

[a]Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, ICG = Inventory of Complicated Grief, TRIG = Texas Revised Inventory of Grief.

no contraindications for the use of bupropion SR and considered appropriate by the principal investigator for treatment with bupropion SR. Diagnoses were made using the Structured Clinical Interview for DSM-III-R (SCID)[4] and confirmed by clinical interview. The intensity of depressive symptoms was measured by the first 17 items of the Hamilton Rating Scale for Depression (HAM-D)[5] (minus the item on sexual symptoms, to be sensitive to the subject's situation) and Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales.[6] Grief was measured with the Texas Revised Inventory of Grief (TRIG)[7] and Inventory of Complicated Grief (ICG)[8] scales. Depression scales were repeated at each visit, whereas grief scales were repeated at the last visit only.

After written and verbal consent statements were obtained, 22 subjects were given bupropion SR, 150 mg/day, for the first week. Bupropion SR was selected as the treatment in this study because of its tolerability and safety in the elderly.[9] It is equally as effective as the serotonin reuptake inhibitors[9,10] and has minimal tendencies for cardiovascular, gastrointestinal, and sedating side effects.[9–11] Subjects were seen weekly for the first month (visits 1–4) and then at 2- and 3-week intervals (visits 5, 6) for a total of 8 weeks of treatment. Depending on response (efficacy and side effects), dose could be increased to 300 mg/day by the second week of treatment. While there was no attempt to provide formal psychotherapy during this study, time was taken in each session to listen to patient concerns and reminiscences of their lost loved one, to provide support and encouragement, and, when appropriate, to help assure the patients that their grief responses were normal. The initial history took about 1 hour, and subsequent rating sessions generally were completed in 25 to 30 minutes. Improvement was measured using the HAM-D and the CGI-S and CGI-I scales for both completer (N = 14) and intent-to-treat (N = 22) samples.

RESULTS

Seventeen widows (77.3%) and 5 widowers (22.7%) entered the study. The mean ± SD age was 63.5 ± 11.0 years, with a range of 45 to 83 years. Four (18.2%) subjects had had at least 1 previous major depressive episode. The mean number of years married was 35.18 ± 15.56, with a range of 5 to 59 years. Nineteen of the subjects were white, 2 were Hispanic, and 1 was African American. At the end of the study, the mean dose of bupropion SR was 250 mg/day for the intent-to-treat sample and 282 mg/day for completers. Reasons for prematurely leaving the study include side effects (N = 4), intercurrent medical illness (N = 1), transportation problems (N = 1), "feeling better" (N = 1), and lack of efficacy (N = 1).

Clinical response is summarized in Table 1. For the completer sample, mean HAM-D-16 scores fell by 73%, CGI-S scores fell by 52%, and CGI-I scores reflected "much/very much improvement" (mean score at last session = 1.79). Similarly, improvement was seen in scores on both grief scales, and correlations between changes in HAM-D-16 and grief scales were in a positive direction. Table 2 shows baseline and end-of-study scores on items of the grief scales that changed by > 20%.

A total of 20 subjects reported at least 1 side effect during the study period. The most common side effects were dry mouth (N = 9), headaches (N = 9), and insomnia (N = 5). Three patients required concomitant hypnotic agents. The side effects that led to premature discontinuation from the study in 4 subjects included insomnia and

Table 2. Inventory of Complicated Grief Items With Changes of > 20% (N = 14)

Inventory of Complicated Grief Item	Baseline	8 Weeks
I feel drawn to places and things associated with the person who died	2.86	2.14
I feel disbelief over what happened	2.86	2.14
I can't help feeling angry about his/her death	2.71	1.79
I feel stunned or dazed over what happened	2.36	1.86
I feel bitter over this person's death	2.36	1.71
Ever since s/he died it is hard for me to trust people	2.00	1.07
Ever since s/he died I feel like I lost the ability to care about other people's feelings or I feel distant from people I care about	1.71	1.14
I feel it is unfair that I should live when this person died	1.57	0.71
I have pain in the same area of my body or have the same symptoms as the person who died	1.29	0.57

flashbacks (in a subject whose husband hanged himself and who had concomitant symptoms of an acute stress reaction), tinnitus and headaches in a second patient who had a history of migraines, restlessness in a third patient who had been quite reluctant to take medications prior to consenting for the study, and dizziness in a fourth patient.

DISCUSSION

The major finding of this study was that significant clinical improvement was observed in most widows/widowers who met DSM-IV criteria for bereavement (i.e., major depressive episodes within 2 months of the death) and were treated with bupropion SR. Treatment did not interfere with grief. On the contrary, modest but significant improvements in grief intensity occurred as depressive symptoms lessened. Bupropion SR appeared safe and well tolerated. This study adds to the literature indicating that tricyclic antidepressants (TCAs)[12–14] and selective serotonin reuptake inhibitors (SSRIs)[15] may ameliorate major depressive disorder associated with bereavement but is the first to suggest a role for active treatment within the first few months of the loved one's death.

Further, combined with the data on the impairment,[1] course,[2] and psychobiology[3] of major depressive episodes seen shortly after the loss of a loved one, the results of this study add to the argument against including bereavement in DSM-V. The loss of a loved one, like any other stressor, can precipitate a major depressive episode in a vulnerable individual. Indeed, it has long been recognized[16] and recently reiterated[17,18] that loss of a loved one is among the most common precipitants of depression. No other life event (or precipitant) negates the diagnosis of depression when the full syndrome occurs. It is not clear why death of a loved one should cancel out the diagnosis of major depressive disorder, either. That there are overlapping symptoms between grief and major depressive episodes should be no more of an impediment to diagnosis than the overlapping symptoms between depression and generalized anxiety, pancreatic cancer, or dementia, all conditions known to be associated with high rates of depression. Calling the depression by another name (i.e., bereavement) may well serve to place the bereaved, depressed individual at risk for prolonged and unnecessary suffering. Rather, when the symptomatic profile, duration of symptoms, and functional impairment warrant it—regardless of time since the loved one's death—the diagnosis of major depressive episode should be made on Axis I and bereavement noted on Axis IV.

Changes in grief scale scores were not as robust as improvement in depression. However, it should be remembered that at the end of the study, approximately 4 months after the loss of a loved one, patients would be expected to still be grieving. Indeed, several patients stated they were better able to grieve (i.e., to begin grieving or allow themselves to grieve more intensely) when they were less depressed. In that vein, a few items on the grief scales (e.g., "I hide my tears when I think about the person who died") increased in intensity over the duration of the study as patients were able to confront situations they had been avoiding when they were more depressed; these changes served to attenuate the value of total change scores on the TRIG or ICG as measures of improvement in this population. Further, it could be that other treatments for depression, such as cognitive-behavioral therapy or interpersonal psychotherapy, would have resulted in a more rapid and robust lessening of grief intensity.

Several methodological limitations of this study caution against considering the results anything but preliminary. First, only 22 of almost 4000 surviving spouses (800–1000 of whom would be expected to meet criteria for major depressive episodes during this time period[1,2,19]) participated in this study. Thus, results may not be generalizable to other populations, especially to diverse ethnic and minority groups. Second, because of the open, noncontrolled design, it is impossible to be sure that the observed changes were due to the effects of bupropion SR or to know whether other factors such as time, support, or heightened expectations might have played significant salutary roles.

Clearly, larger, controlled studies in this highly prevalent and distressed population are warranted. Important questions to be answered include whether treatment of depression improves quality of life and has long-term benefits, what is the most appropriate role for psychotherapy in this population, and whether one specific medication, or class of medications, is best suited for depressive as well as grief symptoms.

Drug name: bupropion (Wellbutrin).

REFERENCES

1. Zisook S, Shuchter SR. Major depression associated with widowhood. Am J Geriatr Psychiatry 1993;1:316–326

2. Zisook S, Paulus M, Shuchter SR, et al. The many faces of depression following spousal bereavement. J Affect Disord 1997;45:85–95
3. Zisook S, Shuchter SR, Irwin M, et al. Bereavement, depression and immune function. Psychiatry Res 1994;52:1–10
4. First MB, Spitzer RL, Williams JBW, et al. Structured Clinical Interview for DSM-IV-Clinician Version (SCID-CV) (user's guide and interview). Washington, DC: American Psychiatric Press; 1997
5. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
6. Guy W. Clinical Global Impressions. In: ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
7. Faschingbauer TR. Texas Revised Inventory of Grief Manual. Houston, Tex: Honeycomb Publishing; 1981
8. Prigerson HG. Inventory of Complicated Grief. In: Van Riezen H, Dublin H, eds. Comparative Evaluation of Rating Scales for Clinical Psychopharmacology. New York, NY: Elsevier Press; 1996
9. Weihs KL, Settle EC Jr, Batey SR, et al. Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. J Clin Psychiatry 2000;61:196–202
10. Croft H, Settle E Jr, Houser T, et al. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. Clin Ther 1999;21:643–658
11. Dunner DL, Zisook S, Billow AA, et al. A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. J Clin Psychiatry 1998;59:366–373
12. Jacobs SC, Kasl SV, Ostfeld AM, et al. The measurement of grief: bereaved vs non-bereaved. Hospice J 1986;2:21–35
13. Pasternak RE, Reynolds CF III, Schlernitzauer M, et al. Acute open-trial nortriptyline therapy of bereavement-related depression in late life. J Clin Psychiatry 1991;52:307–310
14. Reynolds CF, Miller MD, Pasternak RE, et al. Treatment of bereavement-related major depressive episodes in later life: a controlled study of acute and continuation treatment with nortriptyline and interpersonal psychotherapy. Am J Psychiatry 1999;156:202–208
15. Zygmont M, Prigerson HG, Houck PR, et al. A post hoc comparison of paroxetine and nortriptyline for symptoms of traumatic grief. J Clin Psychiatry 1998;59:241–245
16. Holmes T, Rahe R. The social readjustment rating scale. J Psychosom Res 1967;11:213–218
17. Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. Am J Psychiatry 1999;156:837–841
18. Robins LN, Regier DA. Psychiatric Disorders in America: The Epidemiologic Catchment Area Study. New York, NY: Free Press; 1991
19. Clayton PJ. Bereavement and depression. J Clin Psychiatry 1990;51 (7, suppl):34–38