A Post Hoc Comparison of Paroxetine and Nortriptyline for Symptoms of Traumatic Grief

Marianne Zygmont, M.S.; Holly G. Prigerson, Ph.D.; Patricia R. Houck, M.S.; Mark D. Miller, M.D.; M. Katherine Shear, M.D.; Selby Jacobs, M.D.; and Charles F. Reynolds III, M.D.

Background: This report presents the results of an open-trial pilot study of paroxetine for symptoms of traumatic grief, compared with the effects of nortriptyline in an archival contrast group.

Method: Data are presented on 15 subjects (4 men, 11 women), ranging in age from 40 to 79 years (mean age = 57 years), who experienced the loss of a spouse (N = 8), child (N =5), grandchild (N = 1), or parent (N = 1). Subjects were required to have a baseline score on the Inventory of Complicated Grief (ICG) of ≥ 20. Treatment with paroxetine began at a median of 17 months (range, 6–139 months) after the loss. Paroxetine-treated subjects received a psychotherapy tailored for traumatic grief. Depressive symptoms were assessed by using the Hamilton Rating Scale for Depression (HAM-D). The ICG and the HAM-D were administered weekly over 4 months of paroxetine treatment (median dose = 30 mg/day). The group receiving paroxetine were then compared with a group (N = 22) participating in a separate trial of nortriptyline (median dose = 77.5 mg/day) for treatment of bereavement-related major depressive episodes.

Results: Level of traumatic grief symptoms (ICG) decreased by 53%, and depression ratings (HAM-D) decreased by 54% in paroxetine-treated subjects. Nortriptyline showed clinical effects comparable to those of paroxetine.

Conclusion: Paroxetine may be an effective agent in the treatment of traumatic grief symptoms. A comparison of the paroxetine-treated group with a nortriptyline-treated group suggests that both agents have comparably beneficial effects on the symptoms of traumatic grief (as well as those of depression). However, the higher rate of diagnostic comorbidity in the paroxetine-treated group, together with the greater chronicity of their symptoms and the greater safety of paroxetine in overdose, leads us to favor paroxetine over nortriptyline for traumatic grief symptoms in general psychiatric practice. Further controlled evaluation of paroxetine for traumatic grief is necessary.

(J Clin Psychiatry 1998;59:241–245)

Received Oct. 10, 1996; accepted Oct. 27, 1997. From The Mental Health Clinical Research Center for the Study of Late-Life Mood Disorders (Drs. Reynolds, Prigerson, and Miller, Ms. Zygmont, and Ms. Houck) and The Women's Initiative in Services Effectiveness (Dr. Shear), Department of Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, Pa., and the Department of Psychiatry, Yale University, New Haven, Conn. (Dr. Jacobs).

Supported by grants MH-37869, MH-52247, MH-43832, MH-00295 (Dr. Reynolds), MH-53817 (Dr. Shear), and MH-01100 (Dr. Prigerson) from the National Institute of Mental Health, Bethesda, Md.

Reprint requests to: Charles F. Reynolds III, M.D., University of Pittsburgh Medical Center, 3811 O'Hara St., Pittsburgh, PA 15213-2593.

Tricyclic antidepressants (TCAs) have been shown to relieve the symptoms of depression (e.g., depressed mood, apathy, feelings of worthlessness or guilt, psychomotor agitation or retardation) in bereaved adults.[1,2] However, the results of these and other studies have also revealed a discrete set of symptoms coexisting with, but distinct from, depression.[3–5] These symptoms, which we have termed "traumatic" grief, include searching, yearning, preoccupation with thoughts of the deceased to the point of distraction, disbelief regarding the death, feeling stunned by the death, and lack of acceptance of the death.[6] It is not clear whether the symptoms of traumatic grief are effectively mitigated by treatment with TCAs.

Unlike the symptoms of normal grief, those of traumatic grief are not self-limited[3,7,8] and predict long-term functional impairment.[7,9] The presence of traumatic grief symptoms half a year after the loss is associated with disproportionately high rates of physical (e.g., high blood pressure) and psychological (e.g., suicidal ideation) morbidity.[7,9]

Some of the symptoms of traumatic grief are characteristic of posttraumatic stress disorder (PTSD),[6] raising the possibility that treatments effective for PTSD may also be effective for traumatic grief. Conversely, those treatments that have not been effective for PTSD may also not be effective for symptoms of traumatic grief. Although controlled clinical trials of selective serotonin reuptake inhibitors (SSRIs) have not yet been reported, it has been suggested that SSRIs may be more effective than TCAs in the treatment of PTSD.[10,11] SSRIs, therefore, appear to be reasonable candidates in the testing of treatments aimed specifically at the symptoms of traumatic grief.

Table 1. Structured Clinical Interview for DSM-IV (SCID) Diagnoses in Paroxetine-Treated Subjects

Patient No.	Diagnosis
6-Week Completers (N = 15)	
4	Depressive disorder not otherwise specified; posttraumatic stress disorder; history of major depressive disorder
5	Major depressive disorder, recurrent, without psychotic features
7	Minor depressive disorder
9	Generalized anxiety disorder; history of major depressive disorder
10	Major depressive disorder; anxiety disorder not otherwise specified
11	Major depressive disorder; generalized anxiety disorder; panic disorder; posttraumatic stress disorder
13	Depressive disorder not otherwise specified with minor depression
14	Major depressive disorder
15	Major depressive disorder, recurrent; panic disorder without agoraphobia; posttraumatic stress disorder
16	Major depressive disorder, single episode
17	Major depressive disorder, single episode
18	Major depressive disorder, single episode
19	Adjustment disorder with depressed mood
20	Major depressive disorder, recurrent with melancholic features; anxiety disorder not otherwise specified
21	Major depressive disorder, single episode
Dropouts (N = 6)	
1	Major depressive disorder, single episode
2	Adjustment disorder with depressed mood
3	Posttraumatic stress disorder
6	Adjustment disorder; panic disorder; history of major depressive disorder
8	Adjustment disorder; generalized anxiety disorder; history of major depressive disorder
12	Major depressive disorder

The purpose of this report is to present the results of an open-trial study of paroxetine, an SSRI, as a treatment for adults suffering from the symptoms of traumatic grief. The search for a specific treatment is important, given the association between traumatic grief and enduring social and psychological impairment. Also included in this report is an archival contrast between the paroxetine-treated subjects of the present study and the subjects of an ongoing controlled study of nortriptyline, a TCA, for use in alleviating bereavement-related major depressive episodes.[1] The comparison of the 2 groups provides a preliminary test of the hypothesis that SSRIs have specific benefit for traumatic grief symptoms.

METHOD

Twenty-one subjects started treatment; 6 discontinued before completion: 5 because of side effects and 1 because of refusal of further treatment. Fifteen bereaved volunteers (4 men, 11 women; mean ± SD age = 56.9 ± 10.1 years; mean ± SD years of education = 14.4 ± 4.1) completed a 16-week open-trial pilot study of paroxetine for the treatment of traumatic grief. Ten of these volunteers were self-referred, mostly by media ads, and 5 were clinically referred. Eight subjects suffered the loss of a spouse, 5, the loss of a child, and 1 each, the loss of a grandchild or parent. The median time since loss was 16.6 months (range, 6.1–138.6 months). At study entry, the Structured Clinical Interview for DSM-IV (SCID)[12] was used to determine the presence of psychiatric disorders. Most of the subjects were suffering from a major depressive episode (N = 10) or had a history of a major depressive episode (N = 2). Six of the subjects had multiple SCID diagnoses (Table 1). Subjects gave written informed consent after receiving a complete description of the study.

To be eligible for the study, subjects were required to have a score on the Inventory of Complicated Grief (ICG)[6] of ≥ 20. A score of ≥ 20 is considered clinically significant and provides an ample margin for improvement (i.e., a decrease in the score). The ICG was designed to distinguish between normal and more pathologic forms of grief, thus identifying patients at risk for long-term functional impairment. The 18-item ICG assesses the severity of the following symptoms of traumatic grief: being stunned or dazed by the loss, feeling bitter over the death, being preoccupied with thoughts of the deceased to the point of distraction, avoidance of reminders of the deceased, survivor guilt, somatic complaints (particularly identification symptoms), a sense of detachment from significant others, and hallucinations.

Pretreatment evaluation of those accepted into the study was designed to assess severity of traumatic grief symptoms, other psychiatric symptomatology and diagnosis (including depression, anxiety, posttraumatic stress, and substance abuse), general life functioning, cognitive functioning, sleep quality, social rhythm stability, side effects, compliance, social support, self-esteem, and medical burden. Measures were included because of their general relevance to bereavement outcome research and to permit comparisons with other previously reported bereavement studies. Additionally, these measures provide a means of examining risk factors, clinical correlates, and outcomes associated with traumatic grief symptoms and their response to treatment.

The ICG was used to assess the intensity of each subject's symptoms of traumatic grief. Depressive symptoms were assessed by using the Hamilton Rating Scale for Depression (HAM-D).[13] General life functioning was assessed using the Global Assessment Scale (GAS).[14] Further pretreatment evaluation included the Folstein Mini-Mental State Examination (MMSE)[15]; the anxiety index from the Brief Symptom Inventory-Anxiety (BSI-A)[16]; the Pittsburgh Sleep Quality Index (PSQI)[17]; the Impact of Event Scale–Revised: Avoidance, Intrusion, Hyperarousal (RIES-A, -I, -H)[18]; and the UKU Side Effect Rating Scale.[19] Key outcome measures (ICG, HAM-D, GAS, UKU) were repeated weekly. Other measures were repeated at 6-week intervals. Pretreatment evaluation also included laboratory tests of baseline health status: electrocardiogram, complete blood count, liver function tests,

Table 2. Demographic Information for Subjects (N = 15) Who Completed at Least 6 Weeks of Paroxetine Treatment

Age (y) at baseline, mean ± SD (range)	56.9 ± 10.1 (40–79)
Sex, men/women	4/11
Race, white/black	14/1
Education (y), mean ± SD	14.4 ± 4.1
Cumulative Illness Rating Scale total, mean ± SD	7.6 ± 4.1
Time since loss (mo), median (range)	17 (6–139)

metabolic profile, serum albumin level, thyroid function tests, and folate and B_{12} levels. Overall medical burden was assessed using the Cumulative Illness Rating Scale (CIRS).[20]

Patients were treated with paroxetine at an initial dose of 10 mg/day. The dosage was increased weekly in 10-mg increments until a maximum daily dose of 30 mg was obtained. If symptoms were not improving by the sixth week of treatment, the dose was increased to 50 mg/day for the remaining treatment period. The criterion used to determine an increase in dosage was a reduction of the baseline ICG score of less than 25%. The final median dose was 30 mg (range, 20–50 mg). Subjects also participated in the development of "traumatic grief psychotherapy," a new psychosocial intervention tailored specifically for patients with symptoms of traumatic grief. Subjects were seen weekly by a psychiatrist and the psychiatric research nurse for education about traumatic grief, symptom evaluation, and evaluation of side effects and compliance. These evaluations also included orthostatic pulse and blood pressure determinations, weight, and clinical ratings (ICG, HAM-D, GAS, UKU). Initial clinical response was defined through an evaluation of change between pretreatment and posttreatment ICG scores. The minimum treatment duration was 6 weeks.

We compared the paroxetine-treated pilot subjects with nortriptyline-treated subjects participating in a separate ongoing randomized, double-blind, placebo-controlled clinical trial of nortriptyline and placebo in bereavement-related major depressive episodes (projected N = 80). The minimum duration of nortriptyline treatment was 6 weeks. The final median daily dose of nortriptyline was 77.5 mg (range, 50–160 mg). Pretreatment and posttreatment ICG and HAM-D scores were available for 22 nortriptyline-treated subjects (5 men, 17 women; mean ± SD age = 66.2 ± 8.1 years; range, 54–78 years). The median time since loss was 7 months (range, 1–22 months). This group displayed a greater diagnostic homogeneity than did the paroxetine-treated group. By design, the SCID diagnosis for all 22 subjects was major depressive disorder. Only 3 of the subjects were also diagnosed with generalized anxiety disorder.

Comparison of scores from baseline to time 2 (16 weeks) was performed in the 15 paroxetine-treated subjects using Wilcoxon signed rank tests. Change in scores of HAM-D and ICG was compared using a Spearman's rho correlation. The temporal trajectory of symptom decline was compared visually for paroxetine and nortriptyline.

Table 3. Comparison of Outcomes of Clinical Measures at Baseline and After 16 Weeks of Treatment for Subjects (N = 15) Completing at Least 6 Weeks of Paroxetine Treatment*

	Baseline		Time 2 (16 weeks)			Wilcoxon Signed	p
Clinical Measure	Mean	SD	Mean	SD	N	Rank	Value
HAM-D 17-item	19.1	4.8	9.4	6.8	14	45.5	.0002
GAS	56.3	6.6	76.2	9.1	14	45.5	.0002
ICG 18-item	37.7	11.3	19.6	14.6	13	45.5	.0002
PSQI	10.4	5.0	5.7	3.7	11	21.5	.03
RIES 22-item							
Intrusion	24.8	8.9	12.3	8.6	13	42.5	.002
Avoidance	18.4	7.4	10.3	10.7	12	27.0	.02
Hyperarousal	16.0	10.3	8.5	8.1	13	21.0	.04

*Abbreviations: GAS = Global Assessment Scale, HAM-D = Hamilton Rating Scale for Depression, ICG = Inventory of Complicated Grief, PSQI = Pittsburgh Sleep Quality Index, RIES = Impact of Event Scale–Revised.

RESULTS

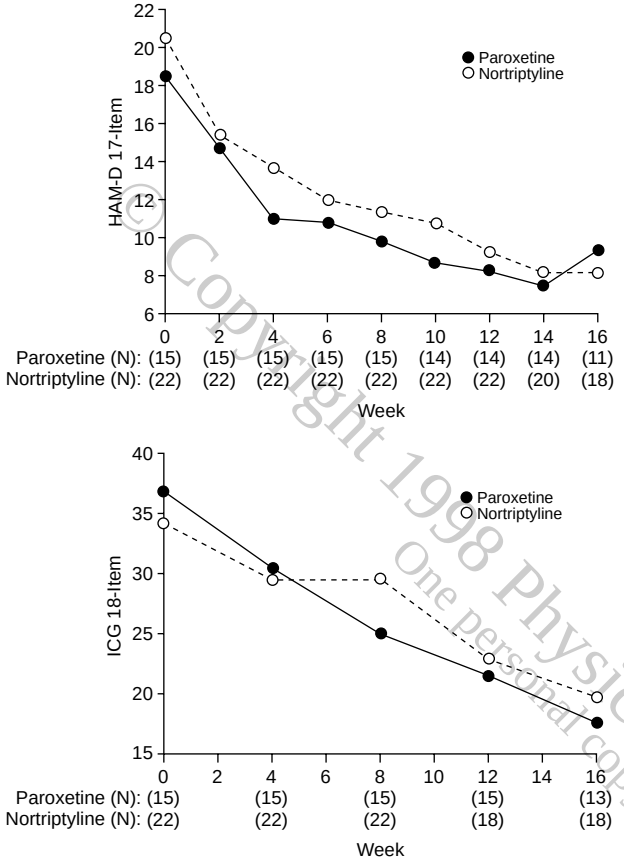
Pretreatment and posttreatment assessments are summarized in Tables 2 and 3. The level of traumatic grief symptoms (ICG) diminished by 53% in paroxetine-treated subjects and depression ratings (HAM-D) by 54%. Subjects experienced a 23% improvement in general level of functioning, with mean GAS scores increasing from 56.3 to 76.2. Self-ratings of avoidant behavior, intrusive thoughts, and hyperarousal (RIES) also improved significantly. The extent of improvement in traumatic grief symptoms was correlated with improvement in depressive symptoms as measured by the correlation between ICG change versus HAM-D change. A positive correlation was found between improvement of these 2 groups of symptoms ($r = .56$, $N = 13$, $p < .05$).

Figure 1 illustrates the temporal trajectory of symptom decline for both HAM-D depression symptoms and ICG traumatic grief symptoms for the 15 subjects who completed at least 6 weeks of the paroxetine open trial and for the 22 subjects who were treated with nortriptyline for at least 6 weeks. Both agents appear to have comparably beneficial effects on the symptoms of traumatic grief; however, there appears to be greater resolution of depressive symptoms than of complicated grief symptoms with both agents.

DISCUSSION

Over the 16-week course of treatment with paroxetine, subjects reported a 50% reduction in symptoms of traumatic grief. While there are limitations in our ability to

Figure 1. Mean HAM-D (Depression, top) and ICG Scores (Grief, bottom) Over 16 Weeks in Paroxetine-Treated Subjects (N = 15) and Nortriptyline-Treated Subjects (N = 22)*



*Sample sizes are presented for each time point to reflect missing data.

compare paroxetine with nortriptyline (open label/archival contrast, post hoc comparison, and psychotherapy confound, as well as other differences between the 2 medication studies), both agents appeared to have comparably beneficial effects on the symptoms of traumatic grief. It should be taken into consideration, however, that the paroxetine-treated subjects were a more diagnostically heterogeneous group; more of these subjects had multiple SCID diagnoses than did those treated with nortriptyline. Additionally, the paroxetine-treated group was more chronically bereft, with the median time since loss more than twice as long as that which characterized the nortriptyline group (16.6 months vs. 7 months).

The use of an SSRI, as an alternative to TCA therapy, was originally suggested by studies investigating the efficacy of TCAs for treatment of bereavement-related depression: traumatic grief emerged as a set of symptoms not greatly affected by pharmacotherapy using TCAs. Pasternak et al.,[1] for example, demonstrated that nortriptyline improved depression scores (HAM-D) by 67.9% in the treatment of 13 bereaved elderly patients, but grief intensity in the group was minimally affected, i.e., TCA treatment was associated with a greater resolution of depressive symptoms than of traumatic grief symptoms. This appears to be the case also with paroxetine treatment, where HAM-D scores dropped more quickly and depressive symptoms appeared to resolve more fully than did traumatic grief symptoms.

The nature of the symptoms of traumatic grief also suggested treatment with an SSRI. The observation by Prigerson et al.[6] of a similarity between symptoms of traumatic grief and PTSD raised the possibility that treatments beneficial for PTSD may also be effective for the treatment of traumatic grief. In their survey of pharmacotherapy for PTSD, Sutherland and Davidson[11] concluded that SSRIs are helpful in the alleviation of PTSD symptoms, effecting enough overall global improvement that some patients no longer met diagnostic criteria for PTSD. Our data, however, suggest comparable benefit for paroxetine and nortriptyline for the symptoms of traumatic grief. Although no specificity of SSRIs for the symptoms of traumatic grief was demonstrated, other factors may, nonetheless, make these agents preferable to TCAs. SSRIs have a relatively benign side effect profile, with fewer of the sedating, anticholinergic, or hypotensive effects associated with TCAs. Additionally, SSRIs are less likely to be lethal in overdose, and plasma levels do not have to be monitored.

Given the morbidity associated with traumatic grief, further prospective studies testing the efficacy and specificity of various treatments are warranted, with random, double-blind assignment and placebo control. Further work is also needed to determine the optimal timing for the assessment of traumatic grief, how long continuation/maintenance treatment should last, rates of relapse on discontinuation of treatment, and how drug treatment compares with psychotherapy.

Drug names: nortriptyline (Pamelor and others), paroxetine (Paxil).

REFERENCES

1. 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
2. Jacobs SC, Nelson JC, Zisook S. Treating depression of bereavement with antidepressants: a pilot study. Psychiatr Clin North Am 1987;10:501–510
3. Kim K, Jacobs S. Pathologic grief and its relationship to other psychiatric disorders. J Affect Disord 1991;21:257–263
4. Pasternak RE, Reynolds CF, Frank E, et al. The temporal course of depressive symptoms and grief intensity in late-life spousal bereavement. Depression 1993;1:45–49
5. Prigerson HG, Frank E, Kasl SV, et al. Complicated grief and bereavement-related depression as distinct disorders: preliminary empirical validation in elderly bereaved spouses. Am J Psychiatry 1995;52:22–30
6. Prigerson HG, Maciejewski PK, Reynolds CF, et al. Inventory of Complicated Grief: a scale to measure maladaptive symptoms of loss. Psychiatry Res 1995;59:65–79
7. Prigerson HG, Bierhals AJ, Kasl SV, et al. Traumatic grief as a risk factor

for mental and physical morbidity. Am J Psychiatry 1997;154:616–623
8. Zisook S, Shuchter SR, Lyons LE. Adjustment to widowhood. In: Zisook S, ed. Biopsychosocial Aspects of Bereavement. Washington, DC: American Psychiatric Press; 1987:51–74
9. Bierhals AJ, Prigerson HG, Fasiczka AL, et al. Gender differences in complicated grief among the elderly. Omega Journal of Death and Dying 1996; 32:303–317
10. Davidson J, Kudler H, Smith R, et al. Treatment of posttraumatic stress disorder with amitriptyline and placebo. Arch Gen Psychiatry 1990;47: 259–266
11. Sutherland S, Davidson J. Pharmacotherapy for posttraumatic stress disorder. Psychiatr Clin North Am 1994;17:409–423
12. First M, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders–Patient Edition (SCID-I/P). New York: New York State Psychiatric Institute; 1995
13. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
14. Endicott J, Spitzer RL, Fleiss JL, et al. The Global Assessment Scale: a procedure for measuring the overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976;33:766–771
15. Folstein MF, Folstein SW, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198
16. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. Psychol Med 1983;13:595–605
17. Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric research and practice. Psychiatry Res 1989;28:193–213
18. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. Psychosom Med 1979;41:209–218
19. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale: a new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl 1987; 334:1–100
20. Linn B, Linn M, Gurel L. Cumulative Illness Rating Scale. J Am Geriatr Soc 1968;16:622–626