Is *DSM-IV* Bereavement Exclusion for Major Depression Relevant to Treatment Response? A Case-Control, Prospective Study

Emmanuelle Corruble, MD, PhD; Bruno Falissard, MD, PhD; and Philip Gorwood, MD, PhD

Objective: The aim of the bereavement exclusion criterion for the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) major depressive episode (MDE) is to identify subjects with a modest, self-limited, "normal" depressive syndrome. One would therefore expect less severe depressive symptoms and a different and better outcome for bereaved subjects who were excluded from the diagnosis of MDE as compared to MDE controls. In a previous cross-sectional study, we have shown such expectations were not met. Herein, we further challenge the accuracy of the bereavement exclusion criterion regarding response to treatment.

Method: In a database of 12,615 subjects seeking treatment for depression, 1,138 (9.0%) individuals met *DSM-IV* MDE criteria except the bereavement exclusion criterion. This sample was matched for age, gender, educational level, and number of previous depressive episodes with 1,138 MDE patients. The bereavement exclusion and MDE groups were prospectively assessed for outcome after 6 weeks of treatment. Primary outcome measures included the number of *DSM-IV* MDE symptoms and the presence/absence of *DSM-IV* MDE Criterion A symptoms at follow-up.

Results: The bereavement exclusion individuals had higher levels of *DSM-IV* MDE symptoms ($P = .005$) and self-rated depression ($P < .0001$) than MDE controls. Both groups had a similar 6-week outcome: 37.7% versus 39.9%, respectively, were responders to treatment, and 80.1% versus 82.2% no longer had the MDE *DSM-IV* symptom criteria at follow-up ($P = .33$).

Conclusions: The *DSM-IV* bereavement exclusion for MDE is inadequate according to response to treatment, at least in this sample of individuals seeking treatment for depressive symptoms. It is proposed that bereavement, just as any stressful event, could be noted but without its affecting the treatment decision.

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Corresponding author: *Emmanuelle Corruble, MD, PhD, Department of Psychiatry, Bicêtre University Hospital, 78 rue du General Leclerc–94275 Le Kremlin Bicêtre, France (emmanuelle.corruble@bct.aphp.fr).*

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) bereavement exclusion for major depressive episodes (MDEs) acknowledges that bereavement may induce a normal response of variable intensity to attachment losses, with a "normal" depressive syndrome that should not be prematurely classified and treated as major depression.[1–3] This exclusion is an attempt to prevent misdiagnosing "normal reactions to bereavement" as disorders.[4,5] Even if grief is different from depression, because the hallmark of grief is longing and yearning rather than sadness and loss of interest and pleasure, however, bereavement, as well as other life events, may sometimes trigger genuine mood disorders,[6–8] the response being symptomatically out of proportion even to loss of a loved one. Thus, excluding all cases of bereavement from MDE may yield false-negative diagnoses. The *DSM-IV* addresses this problem by using the Criterion E bereavement exclusion for MDE, which classifies bereavement responses as MDEs if the symptoms last more than 2 months or if there is marked functional impairment and symptoms such as suicidal ideation. Whatever the accuracy of the 3 former features, proposing exclusion conditions for the E exclusion criteria is at least not straightforward. The relevancy of the E exclusion criteria is therefore to be further analyzed.

Several recent articles have indeed challenged the validity of the *DSM-IV* MDE bereavement exclusion. It has been emphasized that bereavement is the only stressful life event that can lead to exclusion from a *DSM-IV* MDE diagnosis.[9] Two comprehensive literature reviews[10,11] have underlined the similarities between "bereavement related depression" and "non–bereavement related depression," suggesting that the *DSM-IV* bereavement exclusion for MDE is not clinically meaningful. Moreover, 2 recent studies, the first one by Kendler et al[12] in a large-population-based sample of American twins and the second one by Karam et al[13] in a prospective nonwestern culture community sample, also argued for the existence of large similarities between "bereavement-related depression" and "non–bereavement-related depression." Finally, the question of whether, when, and how bereaved people should be treated arises from this literature.[14]

According to the traditional distinction between MDE and normal intense sadness following grief, a clear difference in the number and the type of depressive symptoms, with fewer severe symptoms and a different and better outcome, should be observed for bereaved subjects who were excluded from the diagnosis of MDE as compared to MDE controls. In a previous cross-sectional study,[15] we have shown that this distinction did not apply. In fact, bereavement-excluded subjects were more severely depressed than MDE controls without bereavement and similar to MDE controls with bereavement. Herein, we further challenged the accuracy of the Criterion E exclusion in an independent sample of 1,138 individuals treated as outpatients and followed up for 6 weeks, theoizing that their treatment response would be better than that of a matched group of MDE controls.

METHOD

The rationale and detailed methods of the study and the sample are described elsewhere.[16] One thousand eight

hundred forty-four medical doctors included at least 1 depressed patient in the study. Clinicians were asked to include consecutive patients for whom a new (or different) prescription of antidepressant had to be written for a major depressive episode. The inclusion criteria were being over 18 years old, speaking fluent French, possessing a social security number, being able to give informed consent, and having 5 or more symptoms of the *DSM-IV* diagnosis of MDE, one of which had to be depressed mood or loss of interest most of the day, nearly every day. Exclusion criteria were the diagnosis of bipolar disorder and the use of a mood stabilizer in treatment. After complete description of the study to the subjects, written informed consent was obtained. The *DSM-IV* criteria for an MDE were recorded by the clinician after the 2 face-to-face visits, at baseline and after the follow-up of 6 weeks (a mean duration of 42 days, SD = 8.9). Doctors had a prestudy training session about *DSM-IV* MDE criteria, including the bereavement exclusion criterion. Moreover, they had to assess each MDE criterion (yes/no) to check the diagnosis of MDE. However, no specific instruction was given on the bereavement exclusion prior to the study. The study was naturalistic, and doctors were asked to treat patients "as usual." All antidepressants (in accordance with the French European Medicines Agency) were accepted, in order to reflect usual clinical practice. Any change of antidepressant, an increase in the dosage, or the addition of a benzodiazepine was recorded at the second visit.

From the 12,615 detected patients, 9,515 were initially included as fulfilling the inclusion criteria and not meeting any exclusion criteria.[16] In the present study, we chose to analyze the 1,138 patients who fulfilled the *DSM-IV* MDE A, B, C, and D criteria but who could not be included in the first study because of the E exclusion criterion. Within this sample, a case-control study was designed.

Study Participants

Of the total of 12,615 detected subjects, 1,138 patients (9.0%) were identified as bereavement-excluded individuals, meeting all *DSM-IV* criteria for an MDE except the criterion E bereavement exclusion (BE group). The BE group was older, being a mean (SD) age of 49.5 (14.8) years versus 47.9 (14.2) years ($t = 3.48$; $P = .0005$) and had a mean (SD) number of previous depressive episodes that was less than the rest of the sample (0.67 [1.18] versus 0.96 [1.38], respectively; $t = -6.37$; $P < .0001$; n = 11,477). On the basis of the available literature showing that bereaved individuals with a younger age,[17,18] female gender,[6,19,20] or a prior history of major depressive disorder (MDD)[18] are more likely to develop MDE compared to other bereaved individuals, the 1,138 individuals of the BE group were matched on a 1:1 basis for age, gender, number of previous major depressive episodes, and educational level with 1,138 patients of the rest of the sample (n = 11,477) fulfilling all *DSM-IV* MDE criteria (MDE group).

Instruments

The instruments used in this study are described elsewhere.[16] Briefly, the criteria for an MDE were examined by the clinician during the 2 face-to-face visits. The initial assessment also included the number of past depressive episodes. The Hospital Anxiety and Depression Scale (HADS)[21] was chosen as a self-report instrument to measure symptom severity because of its rapidity and simplicity of rating. The scale was completed by all patients at the first and second visits.

The primary outcome measures selected a priori were the number of *DSM-IV* MDE symptoms at follow-up, the presence/absence of the *DSM-IV* Criterion A symptoms at follow-up, and the variations in depression and anxiety self-assessment scores of the HADS. The secondary measures selected a priori were the 9 *DSM-IV* MDE symptom criteria rated as present or absent at baseline and follow-up.

Statistics

Variables were examined for the normality of distribution before using parametric statistics.

For primary outcome measures, multivariate analyses adjusted for the delay between the 2 visits and marital status were performed: type III sums of squares were estimated from linear models (SAS, PROC GLM; SAS Inc, Cary, North Carolina), containing terms for group (BE or MDE), time (baseline or follow-up), group × time interaction, a fixed subject effect nested in group, and the covariates that determined the pairing and marital status (see below). A logistic conditional regression to study whether the classification in the BE or MDE groups had an impact on the presence/absence of the *DSM-IV* MDE Criterion A symptoms at follow-up was also computed.

For secondary measures, bivariate analyses were performed to examine differences between BE and MDE groups at baseline and follow-up using McNemar tests.

All tests were 2-tailed. For the primary measures, statistical significance was set at an α level of .05. For the secondary measures (the 9 *DSM-IV* MDE symptom criteria), in order to control for type I error due to the number of comparisons, Bonferroni corrections were applied, statistical significance being set at an α level of .005.

RESULTS

Sample

Among the 2,276 individuals of the BE and MDE groups, women constituted 68.4% of the sample, the mean age at inclusion was 49.3 years (SD = 14.7), and the mean number of previous depressive episodes was 0.67 (SD = 1.2). Education levels (low = less than high school, middle = high school graduate, high = more than high school) were as follows: low, 45.3%; middle, 30.6%; and high, 21%.

The BE and MDE groups were not significantly different in terms of employment status, antidepressant drugs, antidepressant doses, antidepressant change between baseline and follow-up, antidepressant dose change between baseline and follow-up, and benzodiazepine prescriptions (Table 1). However, the BE group had a higher frequency of widowed individuals and a lower frequency of married individuals

Table 1. Comparison of Bereavement-Excluded (BE) and Matched Major Depressive Episode (MDE) Groups for Sociodemographic and Treatment Characteristics[a]

Characteristic	BE Group	MDE Group	χ^2	*P*
Marital status, %			97.1	< .0001
Single	16.1	6.6		
Married	45.0	56.5		
Divorced	12.7	16.0		
Widowed	25.7	10.2		
Employment status, %			5.4	.36
Active	54.0	53.1		
Unemployed	9.8	11.2		
Retired	24.0	22.9		
Student	0	0.1		
Other	8.4	9.9		
Antidepressant change between baseline and follow-up, %	10.8	10.4	3.4	.17
Antidepressant dose change between baseline and follow-up, %	15.8	15.5	3.5	.50
Benzodiazepine prescription, %	48.9	46.9	3.4	.49

[a]n = 1,138 for the BE and MDE groups.

than the MDE group (Table 1). Thus, marital status was introduced as a covariate in multivariate analyses.

DSM-IV MDE Symptoms

Whereas all patients fulfilled the *DSM-IV* MDE Criterion A symptoms at baseline, 80.9% of the BE group and 82.2% of the MDE group no longer fulfilled them at follow-up, ie, after 6 weeks of antidepressant treatment (Table 2). As shown by a logistic conditional regression, no group effect ($P = .33$) was observed for the presence/absence of the *DSM-IV* MDE Criterion A symptoms at follow-up.

General linear models for the number of *DSM-IV* MDE symptoms showed a significant time effect ($P < .0001$) and a significant group effect ($P = .005$) but no significant group × time interaction ($P = .83$). The estimated regression coefficient of the group variable was 0.13. The BE and MDE groups had similar outcome based on the number of *DSM-IV* MDE symptoms and the presence of the *DSM-IV* MDE Criterion A symptoms at follow-up. This outcome is characterized by a decrease in the number of *DSM-IV* MDE symptoms over time. After adjustment for other variables, the BE group had a mean number of MDE symptoms 0.13 higher than the one observed in the MDE group.

Regarding specific *DSM-IV* MDE symptoms (Table 3), suicidal ideation was more frequent in BE subjects (36%) than in matched MDE controls (26%). The BE group had also more appetite/weight changes than the MDE controls.

Self-Assessment

The self-rating HADS scores at baseline and follow-up are shown in Table 2. Both BE and MDE groups had relatively high levels of depression and anxiety at baseline. Scores decreased between baseline and follow-up, 37.7% of the BE group and 39.9% of the MDE group being responders to treatment (having at least a 50% decrease in the HADS depression score between the 2 visits).

Results of general linear models for the HADS depression scores showed a significant time effect ($P < .0001$) and a significant group effect ($P < .0001$) but no significant group × time interaction ($P = .90$). The estimated regression coefficient of the group variable was 0.6.

Results of general linear models for the HADS anxiety scores showed a significant time effect ($P < .0001$), no significant group effect ($P = .08$), and no significant group × time interaction ($P = .11$).

Consequently, the BE and MDE groups had similar outcome based on self-rated HADS depression and anxiety scores, with a decrease of these variables over time. Moreover, both groups had similar self-rated anxiety scores. But, after adjustment for other variables, the BE group had an even higher level of self-rated depression (a mean difference of 0.6 points higher) and self-rated anxiety than the MDE group.

DISCUSSION

The discriminant validity of the *DSM-IV* MDE bereavement exclusion seems inappropriate for treatment response in this sample of individuals seeking treatment for depression and treated as usual. Indeed, patients with versus without the *DSM-IV* MDE bereavement exclusion criterion are not different in terms of 6-weeks outcome, bereavement excluded patients being even more severe for some aspects, such as initial suicidality and self-rated level of depression. This result challenges the hypothesis that depressive episodes occurring after a recent bereavement should be considered differently from a true, full MDE, because the patient has fewer chances to get appropriate treatment as a consequence. These results also suggest that almost 10% of the patients with major depression in this sample would be left untreated if the bereavement exclusion were followed.

To our knowledge, this study is the first to assess the discriminant validity of the *DSM-IV* MDE bereavement exclusion by comparing the 6-weeks outcome of depressed patients with and without the MDE bereavement exclusion, the nonbereavement depressed sample being matched for potential confounding factors such as the number of past episodes, gender, and age. The treatment response rate observed for bereaved individuals excluded from the diagnosis of MDE was similar to the response rate of MDE patients.

Our results are in accordance with those showing higher rates of depressive symptoms earlier after bereavement and lower rates later on.[1,2,6,17,18,22] However, these studies have focused mainly on spousal bereavement. Our results extend these findings to several types of bereavement. Moreover, the weak existing evidence in favor of a good treatment response in bereaved individuals is mainly derived from studies based on small sample sizes[23–27] or with no matched control group.[23,25–27] These methodological aspects might have a large impact, as recruiting a small and specific sample dampens the generalizability of the findings. Ten percent of individuals with major depression in our large sample had the Criterion E bereavement exclusion, but the treatment process was not determined by this criterion, increasing the probability that the bereaved patients were representative of clinical outpatients. Furthermore, we had the unique

Table 2. Main Measures for the Bereavement-Excluded (BE) and Matched Major Depressive Episode (MDE) Groups at Baseline and Follow-Up[a]

	Baseline		Follow-Up	
Measure	BE Group	MDE Group	BE Group	MDE Group
DSM-IV MDE symptoms				
Criterion A, %	100	100	19.1	17.8
No. of MDE symptoms, mean (SD)	6.7 (1.3)	6.6 (1.1)	3.0 (2.0)	2.9 (2.0)
Self-assessment: HADS				
Depression score, mean (SD)	14.9 (3.9)	14.2 (3.7)	9.1 (4)	8.5 (3.9)
Anxiety score, mean (SD)	13.5 (3.5)	13.6 (3.4)	9.0 (3.5)	8.7 (3.5)

[a]n = 1,138 for the BE and MDE groups at baseline and follow-up.
Abbreviations: *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; HADS = Hospital Anxiety and Depression Scale.

Table 3. Individual *DSM-IV* MDE Symptoms of Bereavement-Excluded (BE) and Matched Major Depressive Episode (MDE) Groups at Baseline and Follow-Up[a]

	Baseline			Follow-Up		
DSM-IV Criterion	BE Group, %	MDE Group,[b] %	*P*[c]	BE Group, %	MDE Group,[b] %	*P*[c]
A1: sad mood	96.7	96.8	.90	35.5	32.8	.20
A2: loss of interest	96.4	95.6	.34	41.7	40.9	.74
A3: appetite or weight change	54.4	45.5	.0002[d]	23.1	18.7	.01
A4: sleep change	86.1	83.1	.05	38.0	37.1	.58
A5: psychomotor retardation	70.5	72.7	.27	27.1	27.1	.89
A6: fatigue	94.6	95.6	.28	65.5	64.4	.62
A7: worthlessness	66.8	66.7	.97	25.0	24.8	.92
A8: difficulty concentrating	84.0	86.7	.09	41.0	41.0	.99
A9: suicidal ideation	36.0	26.1	<.0001[e]	6.8	4.6	.02

[a]n = 1,138 for the BE and MDE groups at baseline and follow-up. [b]Symptom A1 or A2 must be present for the diagnosis of MDE. [c]Bonferroni correction for multiplicity ($P < .005$). [d]McNemar $\chi^2_1 = 14.1$; statistically significant. [e]McNemar $\chi^2_1 = 25.4$; statistically significant.

opportunity to create a control group matched for core aspects usually considered as reflecting the particularity of the bereaved persons, making it possible to propose some conclusions from the *DSM-IV* MDE bereavement exclusion per se and not just from associated aspects.

Moreover, regarding symptoms at baseline, our results replicate those of a previous cross-sectional study[15] using the same case-control design in a different sample and showing that members of the BE group had more severe depressive symptoms than MDE controls as assessed by clinicians. Accordingly, results obtained on *DSM-IV* suicidal ideation, symptom cue of the *DSM-IV* MDE bereavement exclusion, are in line with the results of the previous study and those of the literature, showing a high rate of suicidal ideation in bereaved individuals, especially those with severe depressive scores.[28–30]

Some limitations of this study have to be acknowledged. First, no specific assessment of the type of bereavement was available in the MDE group. However, regarding the number of patients recruited in this sample, it is expected that all of the different types of bereavement were at least present in the analyses. Second, despite the matching on number of prior episodes, which decreased the likelihood of significant differences in the duration of the current episode, the possibility that the MDE control group may have been a more refractory group of individuals who had a longer duration of the current episode compared to the BE group cannot be ruled out. Third, we do not have data available about prior medication trials to determine whether the control MDE sample had more prior medication failures in the current depressive episode than the bereaved sample. Fourth, another confounding factor might be that the MDE group was likely to have many patients who were reacting to other events (as shown by Wakefield et al[9]) and thus were candidates for responding in a similar pattern to the bereavement group. Fifth, clinicians are very likely to use strategies other than antidepressants, such as counseling, emotional support, psychotherapy, and other treatments potentially as effective as antidepressants for bereaved patients. These nondrug treatments, for which no data are available in our study, may have been uncontrolled confounding factors. Sixth, the duration of follow-up was relatively brief in this study, corresponding to short-term outcomes of depression, with later outcomes being unassessed. Seventh, no double-blind, standardized treatment procedure was applied. Once more, losing the benefit of appropriate controls for confounding factors might be balanced by gaining the benefit of including more patients (because of the ease of such observational studies) and yielding results that are closer to those seen in everyday clinical practice. Nevertheless, a next step would be to perform a double-blind, randomized, controlled study comparing antidepressants and placebo in both BE and MDE control groups, in order to assess the magnitude of the difference between active drugs and placebo in BE subjects and MDE controls. Eighth, our sample of individuals seeking treatment and receiving antidepressants cannot be generalized to community samples. This limitation is important to stress, as the findings of these results are not expected to be completely similar to those in a community sample. Indeed, more severe bereaved patients might ask for care more frequently. On the other hand, the question of treating or not treating a patient with depression, when this episode is associated with bereavement, has to be mainly resolved by clinicians, ie, in treatment settings. Therefore, the results derived from this study may be useful in real life, even if our population may not have been representative of typical clinical samples, especially in terms of number of previous episodes, which was relatively low and did not suggest a chronic or treatment-resistant population compared to most other studies such as the STAR*D. Ninth, this study does not fully address the dilemma of treating bereavement that is accompanied by depressive symptoms with antidepressants and the question of when such treatment might or might not be appropriate. Actually, our results show that many subjects with major depression and bereavement may not receive appropriate treatment. But, on the other hand,

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these results should not minimize the issue of individuals with bereavement who may receive inappropriate antidepressant treatment.

Finally, in this sample of patients seeking treatment, our results show that the 6-week outcome of depressed patients with versus without the MDE Criterion E bereavement exclusion is not different, bereavement-excluded patients being even more severe in some aspects of an MDE, such as initial suicidality and self-rated level of depression. The results of this study, in line with the findings of several clinicians,[10,11,14,31–33] argue against the continued use of the bereavement exclusion criterion in *DSM-5*. If further research confirms these findings, the *DSM-IV* MDE bereavement exclusion should be reconsidered in *DSM-5*, as keeping it means reduced chances of a patient's being correctly diagnosed, living with prolonged and unnecessary suffering, and not getting appropriate treatment. Leaving bereaved people who are depressed untreated could be inhumane at the least and clinically egregious if funding agencies denied reimbursement for these individuals, leaving untreated symptoms that are associated with an increased risk of further psychopathology. It is proposed that bereavement, just as any stressful event, could be noted but without interfering with the treatment decision.

Author affiliations: Department of Psychiatry, Paris XI University, Institut National de la Santé et de la Recherche Médicale (INSERM) U 669, Bicêtre University Hospital, Assistance Publique–Hôpitaux de Paris, Le Kremlin Bicêtre (Dr Corruble); Department of Biostatistics and Public Health, Paris XI University, INSERM U 669, Paul Brousse Hospital, Assistance Publique–Hôpitaux de Paris, Villejuif (Dr Falissard); INSERM U675, Paris VII University (IFR02), and Assistance Publique–Hôpitaux de Paris, Paris, France (Dr Gorwood).

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