Beyond DSM-IV Bereavement Exclusion Criterion E for Major Depressive Disorder

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There are two issues facing the DSM-V in the revision of the criteria for major depressive disorder (MDD), the first being the concept of DSM-III [1] criterion A inclusion symptoms for major depressive episode (MDE), which has recently been addressed by Fava et al. [2], Lichtenberg and Belmaker [3] and Bech [4]. The second concerns bereavement criterion E, which often leads to exclusion from MDE. The rationale behind criterion E was that symptoms of bereavement-related sadness resemble those of major depression without the presence of MDD. Bereavement is the only stressful life event (SLE) which is an exclusion criterion for a DSM axis I diagnosis, unless depressive symptoms associated with bereavement last longer than 2 months or meet the bereavement descriptive E criterion for major depression. Several authors have questioned the validity of excluding bereavement from major depression when all other inclusion criteria are met [5–8]. SLE, including bereavement, have been found to contribute to, initiate and maintain MDD [9–17]. More recently, we reported that DSM-IV bereavement-excluded subjects were more severely depressed than MDE subjects without bereavement, and at least as severely depressed as MDE subjects with bereavement [18]. At this time, the DSM-V is proposing to delete bereavement exclusion criterion E for major depression (www.DSM5.org). In the present ar-

ticle, we propose to revise DSM-IV bereavement exclusion and keep the V code for bereavement as suggested by Paula Clayton [19]. In addition, in the event that criterion E is deleted, we believe that criterion A for major depression should be revised to require at least 7 of the 9 criterion A inclusion symptoms for MDE in all types of MDD, which would satisfy the concerns raised by Lichtenberg and Belmaker [3] and Bech [4] about the overinclusiveness of criterion A, leading to overdiagnosis of MDE. Adjusting the number of inclusion symptoms of criterion A reinforces the dimensional approach to depression initiated by the DSM-III (1980) and DSM-III-R (1987). To avoid a ‘single catchall entity’ diagnosis of MDE [3], depression subtypes can be used, including bereavement depression. Now is the time to reevaluate depression subtypes and MDD, and allow subtypes for some of the well-defined stress event depressions.

Bereavement and Major Depression

Bereavement is known to be associated with high rates of MDE and of other major depressive syndromes [20–29]. Major depression is common during the first year of bereavement, with higher rates earlier in bereave-

ment and lower rates throughout the year following the loss of a loved one [21, 22, 27, 30, 31]. In a prospective study of 109 widows and widowers, 35% of the widows and widowers were depressed after 1 month of bereavement, 25% at 4 months and 17% at 13 months, and 45% were depressed at one point in the year following the death of their spouse [21, 22]. In another study of 350 widows and widowers, 24% ($n = 84$) met DSM-III-R criteria for MDD after 2 months of bereavement, 23% ($n = 72$ of 308) after 7 months and 16% ($n = 46$ of 286) at 13 months [20]. Several authors including Harlow et al. [27] ($n = 136$) and Bruce et al. [24] ($n = 39$) have shown similar increased rates of MDD in bereaved widows and widowers. These studies have mainly focused on spousal bereavement in older or elderly populations. In a later study ($n = 328$), Zisook et al. [30] found a rate of minor depression in widows and widowers of 20% at 2 months after the loss, of 23% at 7 months and of 17% at 13 months. More recently, a high rate of suicidal ideation has been found in bereaved individuals [32–34]. Stroebe et al. [32] compared 60 widowed individuals to married individuals and found that widowed individuals had a greater risk of suicidal ideation, and a higher risk was shown particularly for widows. Suicidal ideation was more likely in bereaved individuals with a prior history of depression [34] and was associated with severe depressive scores [32, 34].

Predictors of Major Depression in Bereavement

Studies looking at factors predicting MDD in bereaved individuals did not report consistent results. Bereaved individuals with a prior history of MDD [30] or psychiatric illness [35, 36] are more likely or at least as likely to develop MDD [21, 22] compared to other bereaved individuals. Age has also yielded conflicting results: some studies have shown younger bereaved subjects being more likely to develop MDD [20, 30], while others have reported an absence of association of age with MDD [21–23, 28, 37, 38]. Women have also been shown to be more likely [24, 38, 39] or as likely to develop MDD [20–23, 28, 30, 37, 40] compared to men after the loss of a loved one. These differences may be due to varying study designs and sample populations. In genetic studies, the vulnerability of individuals to the depressogenic effects of SLE has been linked to the functional polymorphism in the promoter region of the serotonin transporter (5-HTT) [41, 42]. Individuals with the short alleles at the 5-HTT locus showed more major depression, depressive symptoms and suicid-

al ideation associated with SLE than individuals without the short alleles.

DSM Classifications and Bereavement

The DSM classification of bereavement-related major depressive syndromes has evolved over time [43]. Before the DSM-III (1980) [1], the DSM-II (1968) [44] classified neurotic/reactive/bereavement depression as depressive neurosis and endogenous depression as manic-depressive illness, depressed type, related to the presence or absence of an SLE. In the DSM-III, depression following bereavement was described as uncomplicated bereavement (V code) with no classification as a mental disorder, and when bereavement depression met MDE criteria, it was labelled complicated bereavement, which Wakefield et al. [45] proposed to replace by 'complicated bereavement-triggered depression'. In the DSM-IV (1994) [46], bereavement is defined as a V code (V62.82), meaning 'Other Conditions that May Be a Focus of Clinical Attention', and thus, despite the evidence that MDD is often associated with bereavement, major depression in bereaved individuals may not be recognized as a mental disorder. The DSM-IV bereavement exclusion is a leftover of the DSM-II classification of endogenous depression versus neurotic/reactive depression, and thus excludes bereaved individuals, resembling DSM-II neurotic/reactive depression, from the diagnosis of MDD unless depressive symptoms resemble those of DSM-II endogenous depression and last more than 2 months or there is 'marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation'. Therefore, individuals having 5 or more MDE inclusion symptoms of criterion A and showing all other inclusion criteria can be excluded from the diagnosis of MDD and only satisfy the bereavement V code. This goes against the symptom-dimensional approach initiated by the DSM-III, which required 4 inclusion symptoms, and the DSM-III-R with 5 inclusion symptoms for major depression; this should be a major theoretical argument in favour of deleting criterion E.

The rationale for bereavement exclusion was to prevent bereaved individuals who suffer from unpleasant, disturbing, but transient symptoms of depression from being diagnosed as having MDD. However, the risk of underestimating MDD in bereaved individuals is significantly greater and carries clinical consequences for individuals with a DSM axis I disorder.

DSM Axis I and SLE Including Bereavement

The question is raised whether the DSM-IV is justified in separating bereavement from other SLE. Other SLE associated with major depression do not lead to exclusion from the diagnosis of MDD or any other axis I diagnosis. In their literature review, Zisook and Kendler [8] concluded that bereavement-related depression has more similarities than differences with MDD. Several authors [5–8, 47–49] have questioned the validity of excluding bereavement from major depression when all other criteria are met. In contrast, Wakefield et al. [45] proposed to extend the MDD bereavement exclusion to other losses after comparing the 1992 National Comorbidity Survey MDD bereavement exclusion cases ($n = 56$ uncomplicated bereavement-triggered cases) to uncomplicated other-loss-triggered cases ($n = 174$).

Evidence from a French National Cross-Sectional Study

Recently, we reported [18] – based on data from a French national cross-sectional study assessing major depressive symptoms and SLE, carried out between September 2003 and May 2004 – that bereaved individuals excluded from the DSM MDE diagnosis but satisfying all other MDE criteria represented 8.5% ($n = 1,521$) of 17,988 self-referred individuals seeking treatment and meeting DSM MDE inclusion symptom criterion A, and that 74.4% ($n = 13,337$) of the 17,988 participants met the diagnosis of MDE. The methods have previously been described [18]. Briefly, the 1,521 subjects (8.5%) identified as bereavement-excluded individuals, but meeting all other DSM criteria for MDE, were matched by age, gender, marital status, educational level and number of previous depressive episodes with controls coming from the same sample, but meeting all DSM-IV MDE criteria. The MDE module of the Mini-International Neuropsychiatric Inventory (MINI) structured interview [50] was used to complete the diagnostic criteria of DSM-IV MDE, consisting of at least 5 of 9 MDE symptoms including ‘depressed mood’ or ‘diminished interest or pleasure’. In addition, evaluators used the clinical description indicated in the DSM MDE bereavement exclusion to include patients with bereavement in the MDE group. The number of DSM MDE inclusion depressive symptoms of criterion A and the Montgomery-Åsberg Depression Rating Scale (MADRS) [51] assessed the severity of depression. SLE preceding the current depressive syndrome

were identified using the Life Events Inventory (LEI) [52].

Compared to MDE patients from the same sample, bereavement-excluded individuals had significantly more MDE inclusion symptoms and greater severity of depression on the MADRS; we also found that bereaved MDE patients were significantly more depressed than nonbereaved MDE patients [18]. We concluded that there was a high risk of being excluded as bereaved individuals with MDE by physicians: 74.3% (1,789 out of 2,408) in case of general practitioners, and 25.7% (619 out of 2,408) in case of psychiatrists, both using the MINI structured interview and the DSM MDE bereavement exclusion criterion E [18]. In a letter to the editor concerning those results, Clayton [19] wrote: ‘It may be that the instructions are poorly written and that criterion E for major depression should be deleted, but the V code should remain.’

These results suggest that bereavement has specific effects on depression in both MDE bereaved patients and DSM bereavement-excluded individuals, thus providing support for the concept of depression subtypes put forward by Lichtenberg and Belmaker [3] and Bech [4]. We propose that bereavement depression be added as a depression subtype of MDD.

Proposal for Diagnosing MDE in Bereaved Individuals

In this paper, we present data to revise the DSM-IV MDE criteria for bereaved individuals. The proposal consists of using a threshold number of DSM-IV MDE criterion A inclusion symptoms to ensure the severity of depression and to satisfy the DSM-III-R dimensional approach. Bereavement-excluded subjects were divided into 2 groups according to the mean number of MDE inclusion depressive symptoms (6.8; min. 5 to max. 9), one group ($n = 851$) with 7 or more MDE symptoms and the other group ($n = 670$) with less than 7 MDE symptoms. Bereavement-excluded subjects with 7 or more MDE symptoms were found to have significantly ($p < 0.0001$) more of each of the 9 MDE symptoms and higher ($p < 0.0001$) mean total scores on MADRS items compared to those with less than 7 MDE symptoms (Cochran-Mantel-Haenszel χ^2 test and two-sample t test) (table 1). Bereavement-excluded subjects with 7 or more MDE inclusion symptoms were also found to have significantly ($p < 0.0001$) more of each of the 9 MDE inclusion symptoms and higher mean scores on all MADRS items, including the total score, compared to MDE patients meeting all

Table 1. Number and percentages of MDE symptoms, as well as MADRS and LEI scores, in bereavement-excluded individuals meeting all criteria for MDE except bereavement exclusion

	Individuals with ≥ 7 MDE symptoms (n = 851)	Individuals with < 7 MDE symptoms (n = 670)	Test	p
<i>MDE symptoms (9 items)</i>				
Mean number $\pm$ SD	7.74 $\pm$ 0.79	5.61 $\pm$ 0.73	t: -54.1	<0.0001
Depressed mood (a)	99.4%	93.6%	χ^2 : 41.7	<0.0001
Diminished interest or pleasure (b)	98.0%	88.8%	χ^2 : 55.8	<0.0001
Weight disturbance	63.4%	28.9%	χ^2 : 177.4	<0.0001
Sleep disturbance	94.5%	73.9%	χ^2 : 129.5	<0.0001
Agitation/retardation	86.8%	52.1%	χ^2 : 224.1	<0.0001
Fatigue/loss of energy	98.0%	86.6%	χ^2 : 72.8	<0.0001
Worthlessness or excessive guilt	87.3%	49.1%	χ^2 : 263.0	<0.0001
Concentration/indecisiveness	93.5%	69.4%	χ^2 : 152.1	<0.0001
Death or suicidal thoughts	52.5%	18.5%	χ^2 : 186.2	<0.0001
<i>MADRS (10 items)</i>				
MADRS total score (range: 0–50)	33.53 $\pm$ 7.1	28.6 $\pm$ 6.75	t: -13.65	<0.0001
Symptom (a) or (b) must be present for the diagnosis of MDE.				

Table 2. Number and percentages of MDE symptoms, as well as MADRS and LEI scores, in bereavement-excluded individuals meeting all criteria for MDE except bereavement exclusion with 7 or more MDE symptoms and in matched MDE subjects from the same sample

	Bereavement-excluded individuals with ≥ 7 MDE symptoms (n = 851)	Matched subjects with MDE (n = 851)	Test	p
<i>MDE symptoms (9 items)</i>				
Mean number	7.74 $\pm$ 0.79	6.56 $\pm$ 1.19	t: -23.8	<0.0001
Depressed mood (a)	99.4%	95.6%	χ^2 : 24.7	<0.0001
Diminished interest or pleasure (b)	98.0%	93.2%	χ^2 : 23.0	<0.0001
Weight disturbance	63.4%	41.9%	χ^2 : 78.5	<0.0001
Sleep disturbance	94.5%	83.2%	χ^2 : 55.0	<0.0001
Agitation/retardation	86.8%	68.4%	χ^2 : 82.7	<0.0001
Fatigue/loss of energy	98.0%	93.7%	χ^2 : 19.8	<0.0001
Worthlessness or excessive guilt	87.3%	67.7%	χ^2 : 93.3	<0.0001
Concentration/indecisiveness	93.5%	83.6%	χ^2 : 40.9	<0.0001
Death or suicidal thoughts	52.5%	29.3%	χ^2 : 94.0	<0.0001
<i>MADRS (10 items)</i>				
MADRS total score (range: 0–50)	33.53 $\pm$ 7.1	29.9 $\pm$ 6.66	t: -10.71	<0.0001
Symptom (a) or (b) must be present for the diagnosis of MDE.				

DSM-IV criteria for major depression (table 2). Logistic regression analysis was conducted in bereavement-excluded subjects (n = 1,521) to predict 7 or more MDE symptoms, using age, gender, number of previous MDE, MADRS total scores, and LEI total scores as independent

variables. Individuals with 7 or more MDE symptoms were significantly more likely to have higher MADRS total scores (OR: 1.10; 95% CI: 1.08–1.12; χ^2 = 125.13; p < 0.0001) and more previous MDE (OR: 1.10; 95% CI: 1.006–1.21; χ^2 = 4.29; p = 0.03). There were no significant

differences in terms of age (OR: 0.997; 95% CI: 0.99–1.005; $\chi^2 = 0.62$; $p = 0.42$), gender (OR: 1.17; 95% CI: 0.91–1.50; $\chi^2 = 1.61$; $p = 0.20$) or LEI scores (OR: 1.00; 95% CI: 0.99–1.001; $\chi^2 = 0.74$; $p = 0.38$).

Conclusion

The data presented here are in favour of a revised MDE bereavement exclusion criterion to include bereaved individuals with 7 or more MDE inclusion symptoms. The proposed new criterion could be easily determined via the criterion A inclusion symptoms, rather than by the DSM-IV clinical description of ‘marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation’, which, as noticed by Clayton [19], is ‘poorly worded’. The new procedure would have the advantage of being easy to integrate into structured interview questionnaires such as the MINI and the Structured Clinical Interview for DSM-IV since MDE inclusion criterion symptoms are part of the questionnaire for establishing the diagnosis of MDD. It is interesting to note that the results from the logistic regression analysis identified a previous MDE episode as a predictor of the presence of 7 or more DSM-IV MDE inclusion symptoms in bereaved individuals, providing further support for this new approach. Thus, the new criterion for bereavement would include bereaved individuals who have at least 7 MDE inclusion symptoms.

The concept presented here could be extended to the number of inclusion symptoms required for an MDE in

all types of MDD. The DSM-V might require 7 instead of 5 out of the 9 MDE inclusion symptoms of criterion A for MDE. Thus, the patients diagnosed with this new set of criteria would be closer to the more severely depressed MDD patients having participated in clinical trials carried out in the 1978–1990 period by one of the authors (G.C.) [53], and show less of the placebo responses seen in the more recent clinical trials.

The V code for bereavement could be maintained for those who do not meet the proposed inclusion criterion A symptom, and bereavement depression could be classified as a stress event subtype of MDD when bereaved subjects meet the new proposed inclusion criterion A. Lichtenberg and Belmaker [3] proposed 10 subtypes of depression, and Bech [4] kept 3 subtypes of stress event depression, but did not include bereavement depression. We propose the following 6 stress event MDD subtypes: (1) bereavement depression; (2) childhood trauma depression; (3) separation depression; (4) postpartum depression; (5) late-life depression, and (6) seasonal depression. These subtypes could be easily defined. This permits avoiding the ‘single catchall entity’ overinclusiveness and overdiagnosis of DSM-IV MDE criterion A as described by Lichtenberg and Belmaker [3].

Conflicts of Interest

G.C. has received consulting fees and honoraria within the last 5 years from Schering Plough, BioLineRx and Takeda. E.C. has received consulting fees and honoraria within the last 5 years from Servier, Sanofi-Aventis, Bristol Myers Squibb, Wyeth, Lilly, UCB Pharma, Eisai and Janssen-Cilag.

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