Psychological Medicine, 2007, **37**, 779–794. © 2007 Cambridge University Press
doi:10.1017/S0033291707009865 First published online 19 February 2007 Printed in the United Kingdom

REVIEW ARTICLE

Is bereavement-related depression different than non-bereavement-related depression?

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ABSTRACT

Background. This review tackles the question: '*Is bereavement related depression* (*BRD*) *the same or different from standard* (*non-bereavement-related*) *major depression* (*SMD*)*?*' To answer this question, we examined published data on key characteristics that define and characterize SMD to assess whether they also characterize BRD.

Method. We searched all English-language reports in Medline up to November 2006 to identify relevant studies. Bibliographies of located articles were searched for additional studies.

Results. Consistent with the position that BRD is distinct from SMD, some, but not all, studies report that men are as likely as women to have BRD and that past or family histories of SMD do not predict BRD. With greater consistency, studies suggest that, like SMD, BRD is: more common in younger than in older adults, predicated by poor health or low social support, followed by recurrent episodes of major depressive episode (MDE), and associated with impaired immunological responses, altered sleep architecture, and responsivity to antidepressant treatment.

Conclusions. Overall, the prevailing evidence more strongly supports similarities than differences between BRD and SMD. Because so few studies focus on BRD occurring within the first 2 months of bereavement, the period identified by the DSM to exclude the diagnosis of MDE, more research is needed specifically on this group to help us evaluate the validity of this important diagnostic convention.

INTRODUCTION

> Specific external causes very frequently seem to foster the outbreak of melancholia. Some such causes, which can be cited, are physical diseases (influenza, gastritis), operations, losses of fortunes, shock, worries due to business ventures, changes in living conditions, but above all, illness and *death of the next of kin*.
>
> (Kraepelin, 1899/1990)

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Is depression a normal reaction to the death of a loved one? This question, the focus of this review, remains a source of ongoing controversy. We pose the question as:

Is bereavement-related depression (*BRD*) *the same or different from standard* (*non-bereavement-related*) *major depression* (*SMD*)*?*

Since Kraepelin's observation of the importance of bereavement in the pathogenesis of major depressive disorder (MDD), several investigators have provided empirical confirmation. In the Epidemiological Catchment Area Study of Mental Disorders in the United States, for example, Weisman *et al.* (1991) found that 10% of

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all community-dwelling individuals experienced the onset of their depressive syndromes within 1 year of the death of a loved one. These individuals, however, were not diagnosed with MDD because of their bereaved status. Karam (1994) found that 26% of adults in Lebanon who otherwise met criteria for MDD had experienced the death of a loved one within 2 months of the diagnosis. More recently, Cole & Dendukuri (2003), providing a systematic review and meta-analysis of 20 prospective studies on late-life MDD, found that recent bereavement was the most robust risk factor for the onset of a major depressive episode (MDE).

Several studies focusing on bereaved populations have found depressive symptoms, subsyndromal depressive syndromes, minor depression (Zisook *et al.* 1994, 1997), and major depressive syndromes (Clayton *et al.* 1972; Jacobs *et al.* 1989; Bruce *et al.* 1990; Nuss & Zubenko, 1992; Zisook *et al.* 1994; Carnelley *et al.* 1999; Turvey *et al.* 1999; Byrne & Raphael, 1999; Silverman *et al.* 2001; Barry *et al.* 2002; Onrust & Cuijpers, 2006) highly prevalent and often persistent. Major depressive syndromes have been reported in 29–58% of widows and widowers 1 month after their spouse's death (Clayton *et al.* 1972; Gilewski *et al.* 1991; Harlow *et al.* 1991*b*), 20–25% at 2 months (Futterman *et al.* 1990; Zisook & Shuchter, 1991*a*) and 4 months (Clayton *et al.* 1972; McHorney & Mor, 1988), 16–17% at 1 year (Clayton *et al.* 1972; Bornstein *et al.* 1973; Zisook & Shuchter, 1991*b*), and 14–16% at 2 years (Harlow *et al.* 1991*b*; Zisook & Shuchter, 1993*a*). Similar rates have been found in children (Weller *et al.* 1991) and in older adults (Zisook *et al.* 1993; Turvey *et al.* 1999) after the deaths of loved ones.

Despite the well-documented association of bereavement and MDD, BRD historically has been under-recognized and under-treated (Rosenzweig *et al.* 1997). Even today, confusion remains regarding how to distinguish depression form chronic or complicated grief (Lichtenthal *et al.* 2004), and when and how to diagnosis or treat BRD. By evaluating the similarities and differences between BRD and SMD on risk factors, clinical characteristics, course, consequences, biology and treatment, we attempt to clarify this confusion. When the data permits, we pay particular attention to depressive syndromes occurring within the first 2 months of bereavement. This is the time period the DSM-TR (APA, 2000) delineates for bereavement to exclude the diagnosis of MDD.

If BRD is no different than SMD – and especially if BRD occurring within the first few months of the death of a loved one is no different than SMD – the bereavement exclusion for MDE may be invalid.

Brief historical background

Contemporary views of the relationship between loss, grief and depression have their roots in Freudian psychoanalytic theory which holds that grief and depression share many features (Freud, 1957). Lending empirical credence to this concept, a series of studies by Paula Clayton and colleagues a decade before DSM-III documented the high prevalence of major depressive syndromes occurring during bereavement. Thirty-five percent of widows and widowers met criteria for clinical depression 1 month after their spouse's death, and one third of those remained depressed for at least a year. Because these depressive syndromes tended to be relatively mild and 'differed' from clinical depression in several ways, Clayton cautioned against over-diagnosing major depression during the first year of bereavement (Clayton *et al.* 1971, 1972; Bornstein *et al.* 1973; Clayton, 1974; Clayton & Darvish, 1979). Clayton *et al.*'s findings and conclusions served as the forerunners to the DSM-III exclusion of bereavement for the diagnosis of MDE.

DSM-III and DSM-III-R

In DSM-III, 'Uncomplicated Bereavement' was both a V-Code (clinical condition that is *not* a mental disorder) and an exclusion criterion for the diagnosis of MDE. According to DSM-III, 'Uncomplicated Bereavement':

> can be used when a focus of attention or treatment is a *normal* reaction to the death of a loved one. A full depressive syndrome is a *normal* reaction to such a loss, with feelings of depression and such associated symptoms as poor appetite, weight loss and insomnia. The reaction to the loss may not be immediate, but rarely occurs after the first two or three months. The duration of '*normal*' bereavement varies considerably among different subcultural groups (APA, 1980, p. 333).

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To help distinguish 'Uncomplicated Bereavement' from MDE, DSM-III identified features more characteristic of one than the other: (1) a bereaved individual typically regards the depressed mood as 'normal,' although the person may seek professional help for relief of associated symptoms such as insomnia or anorexia; (2) the diagnosis of MDE is generally not given unless the symptoms are still present 2–3 months after the loss; and (3) MDE should be considered in the presence of certain symptoms that are not characteristic of a 'normal' grief reaction, such as *guilt* about things other than actions taken or not taken by the survivor at the time of the death, *thoughts of death* other than the survivor feeling that he or she would be better off dead or should have died with the deceased person, morbid preoccupation with *worthlessness*, marked *psychomotor retardation*, prolonged and marked *functional impairment*, and *hallucinatory experiences* other than thinking that he or she hears the voice of, or transiently sees the image of, the deceased person. Thus, the category of 'Uncomplicated Bereavement' assumed that a full MDE beginning in the first few months after the loss of a loved one and lasting an indeterminate period of time is *normal*.

DSM-IV and DSM-TR

In DSM-IV, 'Uncomplicated Bereavement' was replaced by 'Bereavement'. Other than more sharply delineating the time frame for 'Bereavement' to be 2 months (rather than 2–3 months), there were no substantive changes in diagnostic guidelines. Bereavement remains the only life event that excludes the diagnosis of MDE.

Terminology

Before beginning our literature review, we clarify critical terms. *Mourning* refers to the social and culturally sanctioned rituals related to loss. *Grief* refers to the constellation of feelings, behaviors, cognitions and alterations in functioning attendant upon loss of any kind. *Bereavement* is a specific type of loss, loss from another's death. *Bereavement reactions* refer specifically to grief following the death of a significant other. The DSM-IV added a second definition for *bereavement* – symptoms of MDE occurring within the first few months of the death of a loved one.

The terms – mourning, grief and bereavement – are often used interchangeably, resulting in confusion. To make matters more complicated, several terms are used to describe perturbation in grief (e.g. pathological, morbid, atypical, dysfunctional, unresolved). Recently, much attention has been paid to a syndrome of unusually intense and persistent grief, so-called *complicated* or *traumatic grief* (Horowitz *et al.* 1997; Prigerson *et al.* 1997; Shear *et al.* 2005). Characterized by symptoms of persistent difficulty accepting the death, recurrent pangs of intense grief, preoccupation with thoughts and images of the deceased, and avoidance of reminders of the loss, complicated grief is a different construct than MDD and can reliably be distinguished from it (Prigerson *et al.* 1996; Boelen & van den Bout, 2005). The focus of this review is not complicated grief, *per se*, but rather BRD.

As used in this review, BRD refers to three potentially different groups that are important to distinguish conceptually: (1) individuals who develop symptoms meeting criteria for MDE in the context of the death of a loved one; it often is not specified whether the MDE began shortly before, shortly after, or months after bereavement; (2) individuals who, within 2 months after the loss of a loved one, develop symptoms that technically meet the broad heterogeneous criteria for MDE (i.e. at least 5 out of 9 symptoms lasting at least 2 weeks) but who are considered by the DSM-TR to be experiencing 'normal bereavement'; and (3) individuals who, after the loss of a loved one, also develop symptoms that meet criteria for MDE but whose symptoms are so severe or persistent that the DSM-TR recommends considering the diagnosis of a true MDE rather than just normal bereavement. As we will try to point out, most of the available literature on BRD focuses on Group 1, and therefore can provide only indirect data on the DSM exclusion. There is even less data on Group 3. Wherever possible, this review will highlight results on Group 2, the most pertinent group for the bereavement exclusion criteria.

Summary

In order to answer the question of whether BRD is the same or different from SMD, this review will evaluate whether key characteristics that define and characterize SMD also characterize

https://doi.org/10.1017/S0033291707009865 Published online by Cambridge University Press

BRD. If the predominate weight of the evidence suggests that they do, BRD may be best conceptualized as a form of SMD rather than an extension of 'normal' bereavement.

METHOD

Empirical literature review

Using diagnostic validators as originally proposed by Robins & Guze (1970) and expanded by Kendler (1980), this review evaluates the following null hypothesis regarding the relationship between BRD and SMD: *Based on published data examining predictors, course, clinical characteristics, consequences, biology and treatment of BRD, BRD is similar to SMD*. To test this hypothesis, we examine three classes of potential diagnostic validators, with subclasses as follows:

(1) Antecedent validators

   A. Family studies
   B. Past history of MDE
   C. Demographic factors

(2) Concurrent validators

   A. Health
   B. Social Support
   C. Associated clinical features
   D. Biological variables

(3) Predictive validators

   A. Diagnostic consistency over time
   B. Treatment outcome

Articles for this review were located with Medline searches up to November 2006, English language only, to identify relevant studies with original data. Exploded searches, using 'grief or bereavement' AND depression as keywords were employed. Bibliographies of located articles were searched for additional studies. Publications were selected for inclusion in this review if they included individuals diagnosed with MDE or meeting threshold levels for clinically significant depression based on validated depression interviews or scales. One or more systematic comparison groups were included in most of the studies. Table 1 provides a succinct summary of all studies included in this review. For each study, we present our qualitative assessment of the degree to which it supports or refutes our null hypothesis. This judgment reflects the nature of the finding and the study's methodological rigor, appropriateness of comparison group, and sample size.

If the same sample was presented in more than one publication, only the most relevant or inclusive is examined. The lone exception to this rule is in the categories of family and past history studies where two different studies from Paula Clayton's series of widowhood studies are tabulated because different control groups were used (Clayton *et al.* 1971; Briscoe & Smith, 1975).

For most validating criteria, the ideal comparison group for BRD would be a matched group of SMD. However, few studies compared these two groups directly. Therefore, in the seven Appendix tables we prepared for this review, termed Tables A1–A7 (available in the online version of this paper or at http://geropsych.ucsd.edu/grief), we provide a complete study summary and a categorization of the different comparison groups, which include: (A) comparison of BRD and SMD, (B) comparison of bereaved individuals with non-bereaved controls, (C) comparison of BRD with uncomplicated bereavement, (D) comparison of bereaved individuals to in-patient SMD, (E) study of BRD only, and (F) study of bereaved individuals only.

While it would have been ideal to conduct formal meta-analyses of this literature, this was not feasible. Few primary reports provided confidence intervals (or standard errors) or primary data (i.e. contingency tables or correlations). Data is presented so as to facilitate an integration of results comparing the validators in the groups. Table 2 summarizes the overall results. For each group of validators, a global score is provided summarizing its overall support for the study's hypothesis (I = equivocal; S = supportive; NS = not supportive).

RESULTS

Antecedent validators

Family and past personal history of major depression

Two of the most consistently noted predictors of SMD are family history (Weissman *et al.* 2005), and past personal history of SMD (Lewinsohn *et al.* 1988). Tables 1 and A1 describe nine

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studies assessing the relationships of family and/or past history of SMD and the onset of major depression in recently bereaved individuals. Three of the studies included an SMD control group, but the number of control participants with MDE in each of these studies was small (Briscoe & Smith, 1975; Brent *et al.* 1994; Hays *et al.* 1994*a*). A fourth study included a non-bereaved control group, but since none of the controls had MDE, only comparisons between bereaved individuals with and without MDE are considered (Byrne & Raphael, 1999). Another study (Briscoe & Smith, 1975) included a non-bereaved control group, divorced men and women, as well as in-patients with SMD, and compared both groups to widows and widows previously reported by Clayton and colleagues (Clayton *et al.* 1971, 1972; Bornstein *et al.* 1973; Clayton, 1974; Clayton & Darvish, 1979). However, in-patients with SMD are a questionable comparison group since BRD rarely requires hospitalization. Similarly, one study compared bereaved children to in-patient children with MDD (Weller *et al.* 1991). The remaining three studies primarily compared bereaved individuals with BRD to bereaved individuals without depression (Clayton *et al.* 1971; Jacobs *et al.* 1989; Zisook & Shuchter, 1993*b*).

Of the six studies evaluating family history of depression among those who were bereaved (Tables 1 and A1), three found family history of MDE to be positively associated with BRD (Weller *et al.* 1991; Brent *et al.* 1993; Zisook & Shuchter, 1993*b*). One of the negative studies looked at family history of mood disorder rather than specifically depression (Clayton, 1974). However, in a separate investigation, the 18 widows and four widowers who met syndromal criteria for SMD from Clayton *et al.*'s study (Clayton *et al.* 1972; Clayton, 1974) were compared to 22 age- and sex-matched hospitalized depressives and 43 recently divorced men and women meeting the same diagnostic criteria for syndromal depression (Briscoe & Smith, 1975). Compared to both the hospitalized patients and the divorced depressives, the depressed widows/widowers had fewer first-degree relatives with MDD. This is the only study we found that compared syndromal depression in bereaved individuals to SMD occurring in the context of other adverse life events, but the sample was small and the two groups were poorly matched for age.

Tables 1 and A1 also contain the nine studies examining the relationship of past history of 'depression' and risk for BRD in bereaved individuals. The findings are mixed. One study used past treatment for SMD rather than occurrence of SMD (Clayton *et al.* 1971), and three assessed dysphoria rather than syndromal SMD (Bruce *et al.* 1990; Hays *et al.* 1994*a*; Byrne & Raphael, 1997). Three of the studies that assessed past histories of actual SMD found positive relationships between past SMD and BRD (Weller *et al.* 1991; Brent *et al.* 1993; Zisook *et al.* 1997). One of the studies not only found a relationship between past histories of SMD and BRD, but also reported a significant gradation in risk based on the number of previous MDEs: the rates of BRD at 6–8 weeks post-bereavement for widows and widowers who had never been depressed was 13%, for those who had been depressed once previously was 30%, and for those who had experienced two or more pre-bereavement MDEs was 46% (Zisook *et al.* 1997). On the other hand, one study found fewer episodes of previous SMD in widows and widows with BRD than in comparable groups of in-patients or divorcees with SMD (Briscoe & Smith, 1975).

Demographic factors

The demographic factors most strongly associated with risk for SMD are female gender and young adult age (Kessler *et al.* 2005). Tables 1 and A2 summarizes studies evaluating the associations of these factors with onset of BRD: two studies compared BRD to SMD (McHorney & Mor, 1988; Karam, 1994), two compared bereaved with non-bereaved groups (Gallagher *et al.* 1983; Lichtenstein *et al.* 1996), five compare bereaved with BRD to bereaved who were not depressed (Clayton *et al.* 1971; Richards & McCallum, 1979; McHorney & Mor, 1988; Jacobs *et al.* 1989; Zisook & Shuchter, 1993*a*) and one compared widows and widowers on a depression intensity scale (Lund *et al.* 1986).

Four of eight studies comparing men and women found no gender difference in risk for BRD (Clayton *et al.* 1971; Lund *et al.* 1986; McHorney & Mor, 1988; Zisook & Shuchter, 1993*a*) while three of the remaining four studies

https://doi.org/10.1017/S0033291707009865 Published online by Cambridge University Press

https://doi.org/10.1017/S0033291707009865 Published online by Cambridge University Press

Table 1. *Overview of studies included in the review*

Validators	Studies reviewed	Number of bereaved participants	Number of participants with BRD	Time of assessment in relation to death	Comparison group/type of study[a]	Hypothesis[b]
Antecedent						
Family history	Clayton *et al.* (1971)	109	38	1 mo.	C	NS
	Briscoe & Smith (1975)	109	26	1 mo.	A, D	NS
	Jacobs *et al.* (1989)	111	60	6, 12 mos.	C	NS
	Weller *et al.* (1991)	38 (children)	14	3–12 wk	D	S
	Zisook *et al.* (1997)	328	67	2, 7, 13, 19, 25 mos.	C	S
	Brent *et al.* (1993)	146 (adolescents)	61	1–7 mos.	A, C	S
Past history	Clayton *et al.* (1971)	109	38	1 mo.	C	NS
	Briscoe & Smith (1975)	109	26	1 mo.	A, D	NS
	Jacobs *et al.* (1989)	111	60	6, 12 mos.	C	NS
	Bruce *et al.* (1990)	39	12	6, 12 mos.	A	NS
	Weller *et al.* (1991)	38 (children)	14	3–12 wk	D	S
	Zisook *et al.* (1997)	328	67	2, 7, 13, 19, 25 mos.	C	S
	Brent *et al.* (1993)	146 (adolescents)	61	1–7 mos.	A, C	S
	Hays *et al.* (1994*b*)	207	N.A.	2, 6, 13, 25 mos.	B	S
	Byrne & Raphael (1999)	57	7	6 wks, 13 mos.	C	NS
Gender	Clayton *et al.* (1972)	109	38	1 mo.	C	NS
	Richards & McCallum (1979)	100	29	6 mos.	C	NS
	Gallagher *et al.* (1983)	211	67	2 mos.	B	S
	Lund *et al.* (1986)	192	N.A.	1, 2, 6, 13, 25 mos.	F	S
	McHorney & Mor (1988)	1447	285	Pre, 3–4 mos.	C	NS
	Jacobs *et al.* (1989)	111	60	6, 12 mo.	C	S
	Bruce *et al.* (1990)	39	12	6, 12 mo.	A	S
	Zisook *et al.* (1997)	259	59	2, 7, 13, 19, 25 mos.	C	NS
Age	Gallagher *et al.* (1983)	199	67	2 mos.	B	S
	McHorney & Mor (1988)	1147	285	Pre, 3–4 mos.	C	S
	Jacobs *et al.* (1989)	111	60	6, 12 mos.	C	NS
	Bruce *et al.* (1990)	39	12	Pre, 6, 12 mos.	A	NS
	Zisook *et al.* (1997)	259	59	2, 7,13, 19, 25 mos.	C	S
	Karam (1994)	658	94	2 mos.	A	S
	Lichenstein *et al.* (1996)	269	137	<3, >5 yr	B	S
Concurrent						
Health	McHorney & Mor (1988)	1147	285	Pre, 3–4 mos.	C	S
	Harlow *et al.* (1991*a*)	136	78	1, 6, 12, 18, 24 mos.	F	S
	Zisook & Shuchter (1993*b*)	286	46	2, 7, 13 mos.	C	S
Social support	Clayton *et al.* (1975)	109	38	1, 4, 13 mos.	C	S
	Dimond *et al.* (1987)	192	N.A.	3, 8 wk; 6, 12, 18, 24 mos.	F	S
	McHorney & Mor (1988)	1147	285	Pre; 3–4 mos.	C	NS
	Norris & Murrell (1990)	85	N.A.	Pre, 6 mos.	B	S
	Harlow *et al.* (1991*a*)	136	78	Pre, 1, 6, 12, 18, 24 mos.	F	S
	Nuss & Zubenko (1992)	50	12	6–12 mos.	F	S

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Clinical features	Clayton & Darvish (1979)	149	63	1, 13 mos.	C	S
	McHorney & Mor (1988)	1447	285	Pre, 3–4 mos.	C	S
	Jacobs *et al.* (1989)	39	12	6, 12 mos.	A	S
	Bruce *et al.* (1990)	393	113	Pre, 6, 12 mos.	C	I
	Gilewski *et al.* (1991)	111	60	1, 6, 12, 30 mos.	C	S
	Weller *et al.* (1991)	38 (children)	14	3–12 wk	D	I
	Brent *et al.* (1993)	146 (adolescents)	61	7 mos.	A, B	S
	Zisook & Shuchter (1993*b*)	259	59	2, 13, 25 mos.	C	S
	Karam (1994)	658	94	2 mos.	A	S
	Byrne & Raphael (1999)	57	7	6 wk, 6, 13 mos.	C	S
Biological factors						
Immunologic	Linn *et al.* (1984)	49	N.A.	6 mos.	B	S
	Irwin *et al.* (1987*b*)	10	N.A.	1–6 mos.	B	S
	Zisook *et al.* (1993)	21	6	2, 7, 13 mos.	B	S
	Gerra *et al.* (2003)	14	N.A.	10, 40, 180 days	B	S
Endocrine	Kosten *et al.* (1984)	13	N.A.	6 mos.	F	I
	Shuchter *et al.* (1986)	19	N.A.	2–5 wk	F	NS
	Roy *et al.* (1988)	28	9	5–10 mos.	A, B, C	S
	Weller *et al.* (1990)	18 (children)	N.A.	1 mo.	F	S
Sleep Heart rate variability	Gerra *et al.* (2003)	14	N.A.	10, 40, 180 days	B	S
	Reynolds *et al.* (1992)	31	15	<6 mos.	A, B, C	S
	O'Connor *et al.* (2002)	10	N.A.	2–24 mos.	B	S
Predictive						
Persistence over time	Karam (1994)	658	94	2 mos.	A	S
	Brent *et al.* (1993)	146 (adolescents)	51	1–7 mos.	A, C	S
	Norris & Murrell (1990)	85	N.A.	Pre, 6 mos.	B	S
	Bruce *et al.* (1990)	39	12	Pre, 6, 12 mos.	A, B	S
	Harlow *et al.* (1991*a*)	136	78	1, 6, 12, 18, 24 mos.	B	S
	Mendes De Leon *et al.* (1994)	139	23	Pre, 0–3 yr	B	S
	Hays *et al.* (1994*b*)	207	N.A.	Pre, 2, 6, 13, 25 mos.	B	S
	Bodnar & Kiecolt-Glaser (1994)	49	11	Pre, 1, 1–2, 2+ yr	B	S
	Lichenstein *et al.* (1996)	269	137	<3, <5 yr	B	S
	Turvey *et al.* (1999)	223	31	1, 2–3, 4–6, 7–12, 19–24 mos.	B	S
	Carnelley *et al.* (1999)	64	8	Pre, 12, 24, 36 mos.	B	S
	Wilcox *et al.* (2003)	2254	N.A.	Pre, <1, 1–3 yr	B	S
	Clayton & Darvish (1979)	149	24	1, 13 mos.	C	S
	Lund *et al.* (1985)	192	N.A.	1, 2, 6, 12, 18, 24 mos.	F	S
	Thompson *et al.* (1991)	212	N.A.	2, 12, 30 mos.	B	S
	Stroebe & Stroebe (1991)	60	25	4–7, 14, 24 mos.	B	S
	Zisook *et al.* (1997)	350	59	2, 13, 25 mos.	C	S
Treatment	Jacobs *et al.* (1987)	10	10	1–2 yr	E	S
	Pasternak *et al.* (1991)	13	13	2–25 mos.	E	S
	Reynolds *et al.* (1999)	80	80	6–18 mos.	E	S
	Zisook *et al.* (2001*b*)	22	22	6–8 wk	E	S
	Oakley *et al.* (2002)	10	10	3 mos.	E	S

[a] Type of comparison group: (A) BRD *v.* SMD; (B) bereaved individuals *v.* non-bereaved controls; (C) BRD *v.* uncomplicated bereavement; (D) bereaved individuals *v.* in-patient SMD; (E) BRD only; (F) bereaved individuals only.

[b] S, Supports hypothesis; NS; does not support hypothesis; I, inconclusive.

Table 2. *Summary of evidence for hypothesis (BRD is similar to SMD)*

Feature	Hypothesis[a]
Antecedent validators	
Family history MDD	I
Past history MDD	I
Gender	I
Age	S
Concurrent validators	
Health	S
Social support	S
Clinical features	S
Immunologic studies	S
Endocrine studies	I
Sleep studies	S
Predictive validators	
Persistence over time	S
Treatment	S

[a] S, Supports hypothesis; I, inconclusive.

reported that women were more likely than men to experience BRD (Gallagher *et al*. 1983; Jacobs *et al*. 1989; Bruce *et al*. 1990). One small study reported men to be at greater risk (Richards & McCallum, 1979). Another large study of older adults (not included in Table A2 because it did not provide statistical comparisons between men and women), found women to have more depression than men shortly pre-bereavement (26% *v*. 15%), while men had more depression during the first year of bereavement (46% *v*. 32%) (Mendes De Leon *et al*. 1994).

Results of studies examining the association of age with BRD were also mixed. Five of six studies reported increased rates of BRD in younger individuals (Gallagher *et al*. 1983; McHorney & Mor, 1988; Jacobs *et al*. 1989; Bruce *et al*. 1990; Zisook & Shuchter, 1993*a*; Lichtenstein *et al*. 1996), while one study reported no difference (Bruce *et al*. 1990). Performing a house-to-house survey in Lebanon, Karam (1994) found no differences in the age of onset of 94 individuals with BRD and 281 non-bereaved individuals with SMD.

Antecedent validators in subjects within 2 months of bereavement

To address as directly as possible the validity of the bereavement exclusion for the diagnosis of MDD, it is important to evaluate bereaved individuals who meet symptomatic criteria for MDE within 2 months of the death of a loved one but who are considered by the DSM-TR to be experiencing 'normal bereavement'. Of the two studies that evaluated family history and past personal history of MDE, one supported the major hypothesis we are evaluating – that BRD resembles SMD (Zisook *et al*. 1997) – and one did not (Clayton *et al*. 1972). One of four studies that evaluated gender supported this hypothesis (Gallagher *et al*. 1983) and three did not (Clayton *et al*. 1971; Lund *et al*. 1986; Zisook *et al*. 1997). In contrast, each of the three studies that evaluated age or age of onset provided support for the hypothesis that SMD closely resembles SMD (Gallagher *et al*. 1983; Zisook & Shuchter, 1993*a*; Karam, 1994). Overall, then, it does not appear that the antecedent validators of family and past personal histories of MDD or gender or age provide consistent evidence for or against the close similarity between BRD and SMD.

Concurrent validators

A number of environmental, clinical and biological features characterize SMD. Two important concurrent risk factors for SMD are poor physical health (Barkow *et al*. 2002) and low social support (Kendler, 1999). Some of the clinical features that are associated with SMD are characteristic symptoms (Gaynes *et al*. 2005), dysfunction and disability (Judd *et al*. 2000), and suicidality (Sokero *et al*. 2005). Biological factors that often are seen in SMD include adrenocortical dysregulation (Nemeroff, 1998), immune dysfunction (Dunn *et al*. 2005) and sleep architecture disruption (Reynolds & Kupfer, 1987).

Health and social support

Tables 1 and A3 summarize seven studies presenting data on physical health and/or social supports and the subsequent onset of BRD. None of these studies compared BRD to SMD. One of the studies compared bereaved to matched non-bereaved individuals (Norris & Murrell, 1990), three compared bereaved persons with BRD to those without depression (Clayton, 1975; McHorney & Mor, 1988; Zisook & Shuchter, 1991*b*) and three examined bereaved populations without comparison groups (Dimond *et al*. 1987; Harlow *et al*. 1991*a*; Nuss & Zubenko, 1992).

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All three studies assessing health and/or physical limitations found significant relationships between poor health and onset of BRD (Clayton, 1975; McHorney & Mor, 1988; Harlow *et al.* 1991*a*; Zisook & Shuchter, 1991*a*). Five of six studies measuring social support found an inverse relationship between social supports and BRD (Clayton, 1975; Dimond *et al.* 1987; Norris & Murrell, 1990; Harlow *et al.* 1991*a*; Nuss & Zubenko, 1992).

Associated clinical features

Clinical features associated with BRD are summarized in Tables 1 and A4. In the only two studies that compared adults with BRD and SMD (Bruce *et al.* 1990; Karam, 1994), more similarities than differences were noted between the two groups. Comparing newly bereaved men and women with prospectively defined BRD to married men and women with SMD, Bruce *et al.* (1990) reported similar rates of psychomotor changes and suicidal ideation, but lower rates of guilt and worthlessness in those with BRD. Karam (1994) reported that the two syndromes were indistinguishable in terms of duration of episodes, degree of dysfunction, and help-seeking behaviors. In a study of adolescent bereavement, Brent *et al.* (1993), also included a control group of non-bereaved adolescents, but there were too few with SMD to provide meaningful comparisons with bereaved adolescents who had BRD. However, that study did report that the 43 adolescents with BRD had high rates of several features known to characterize SMD: co-morbid PTSD, impaired functioning and suicidality.

Since psychomotor retardation, feelings of worthlessness and suicidal ideation are symptoms purported to discriminate between normal bereavement and bereavement complicated by major depression in the DSM-III, -III-R, -IV and -TR, studies that describe the presence or severity of those symptoms in BRD are included. In addition to the two studies described in the preceding paragraph (Bruce *et al.* 1990; Karam, 1994), five other relevant reports were found. Bornstein *et al.* (1973) reported over a third of recently bereaved widows and widowers who met syndromal criteria for BRD felt 'worthless and no good', 56 had death wishes and 7% expressed suicidal ideation. Suicidal ideation and feelings of worthlessness were two of the few depressive symptoms that did not decrease over the first year of widowhood (Bornstein *et al.* 1973). Jacobs *et al.* (1989) found that BRD at 6 and 12 months were associated with anxiety, psychomotor retardation and other melancholic features. Zisook *et al.* (1993) reported significantly higher rates of feelings of worthlessness and thoughts of ending one's life among widows and widowers with BRD compared to those without BRD or married controls. In a study of older widowers, Byrne & Raphael (1999) reported high rates of psychomotor disturbance, feelings of worthlessness and suicidal ideation among widowers with BRD *versus* non-depressed widowers.

Studying 38 prepubertal children who experienced death of a parent and 38 matched in-patient depressed control children, Weller *et al.* (1991) reported the most frequent symptoms experienced by all of the bereaved children were: dysphoria (61%), suicidal ideation (61%), loss of interest (45%), psychomotor agitation or retardation (37%), guilt/worthlessness (37%). The occurrence of individual depressive symptoms was reported less frequently by the recently bereaved children than by in-patient depressed children but the overall pattern of symptoms was similar. Unfortunately, no comparisons were made between the depressed in-patient children and the subgroup of bereaved children who met symptom criteria for major depression to see how symptoms in these two groups compared.

Biological factors

Developments in bereavement biology have occurred on three major fronts: endocrinologic responses, immunologic changes and physiologic studies. Each of these domains could serve as external validators to evaluate our key hypothesis.

SMD has been associated with several perturbations in various biological systems. For example, endocrinologic studies have demonstrated adrenocortical dysregulation and overactivation in patients with SMD (Carroll *et al.* 1981; Lesch *et al.* 1988). Impaired immune function also has been identified an important feature of SMD (Schleifer *et al.* 1984). One of the most consistent findings found in patients with SMD has been alterations in sleep architecture (e.g. decreased rapid eye movement

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latency and deep sleep duration) (Kupfer *et al.* 1991). More recently heart rate variability, an important mediator of health and disease, has been found to be decreased in SMD (Rechlin *et al.* 1994). The studies, highlighted in Tables 1 and A5, include: two studies comparing subjects with BRD to those with SMD (Roy *et al.* 1988; Reynolds *et al.* 1992), one study comparing bereaved individuals to depressed and non-bereaved controls (O'Connor *et al.* 2002), four studies comparing bereaved to matched non-bereaved samples (Linn *et al.* 1984; Irwin *et al.* 1987; Zisook *et al.* 1993; Gerra *et al.* 2003), and three studies evaluating bereaved elderly adults (Kosten *et al.* 1984), adults (Shuchter *et al.* 1986; Weller *et al.* 1990) and children that did not include control groups.

Four of the studies summarized in Tables 1 and A5 assessed the dexamethasone suppression test (DST) in bereaved individuals. Rates of non-suppression were 0% (Kosten *et al.* 1984), 16% (Shuchter, 1986), and 36% (Weller *et al.* 1990) in the three relevant studies. The fourth study reported blunted mean cortisol levels in bereaved *versus* non-bereaved groups (Gerra *et al.* 2003). In two of the studies, cortisol levels (Kosten *et al.* 1984) or abnormal DSTs (Gerra *et al.* 2003) were directly related to severity of depression. None of these studies assessed depressed controls. In contrast, one small study measuring adrenocorticotropin (ACTH) response to corticotrophin-releasing hormone (CRH) did employ a depressed control group and reported that subjects with BRD demonstrated ACTH responses to CRH similar to those with SMD, and distinct from bereaved individuals without BRD and normal controls (Roy *et al.* 1988).

Four studies assessed immune function in patients with BRD. Three of the studies found impaired immune function related to depression symptom severity (Linn *et al.* 1984; Irwin *et al.* 1987; Gerra *et al.* 2003) and the fourth found abnormal immune function only in the subset of bereaved individuals with BRD (Zisook *et al.* 1993).

Two studies assessed physiologic measures in BRD and both included controls with SMD. In the first, sleep patterns were measured in patients with BRD, depressed controls and normal controls; only the subgroup of bereaved subjects with BRD had abnormal sleep architecture. Their sleep resembled individuals with recurrent MDD and differed from other bereaved individuals without BRD (Reynolds *et al.* 1992). In the second study, heart rate variability (HRV) was decreased in bereaved individuals in direct relationship to levels of depression.

Concurrent validators in subjects within 2 months of bereavement

In subjects within 2 months of bereavement, BRD was associated with poor health (Harlow *et al.* 1991; Zisook & Shuchter, 1991*b*) and social support (Clayton *et al.* 1975; Dimond *et al.* 1987; Harlow *et al.* 1991*a*). In addition, compared to bereaved individuals without BRD within 2 months of the loss, those with BRD had more suicidal thoughts, feelings of worthlessness and psychomotor disturbances (Clayton & Darvish, 1979; Bruce *et al.* 1990; Zisook *et al.* 1993; Byrne & Raphael, 1999), though not so in comparison to hospitalized patients with SMD (Weller *et al.* 1991). Thus, symptoms that the DSM specifically states should raise consideration for the diagnosis of MDD, even in the face of recent bereavement, often characterize the depressive syndromes of recently bereaved individuals. In this way, BRD may resemble SMD more than it resembles 'uncomplicated bereavement'. Similarly, the four studies that evaluated biological parameters within the first 2 months of bereavement mostly supported the similarity of BRD with SMD. Two found immunologic changes in bereaved adults to resemble these reported in SMD (Zisook *et al.* 1994; Gerra *et al.* 2003). One study in adults with BRD (Gerra *et al.* 2003) and another in children with BRD (Weller *et al.* 1991) found DST non-suppression in recently bereaved individuals to correlate with depression symptom severity while one study found DST non-suppression more associated with anxiety than with depressive symptoms in recently bereaved widows and widowers (Shuchter *et al.* 1986).

Predictive validators

Diagnostic consistency over time

Tables 1 and A6 summarize studies examining the persistence over time of BRD. Table A6 is divided into three sections. First are two studies directly assessing whether BRD predicts future SMD. Studying an adult community population

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in Lebanon, Karam (1994) found that BRD was as likely as SMD to predict future SMD. In a study of adolescents losing a close friend to suicide, Brent *et al*. (1994) also reported that BRD predicts future SMD. Like Karam (1994), Brent *et al*. (1994) also reported that the mean durations of BRD were similar to those reported for SMD.

Tables 1 and A6 also summarize ten studies that evaluated bereaved individuals both before and after the deaths of loved ones. Those studies found uniformly higher rates of depressive syndromes than in non-bereaved controls lasting well beyond the first several months after bereavement. Several of those studies reported that symptoms of depression often began months to years before the actual death (Norris & Murrell, 1990; Harlow *et al*. 1991*b*; Lichtenstein *et al*. 1996; Carnelley *et al*. 1999). It is not clear to what extent the 'persistence' of BRD in these studies represents recurrent *versus* chronic depression. In either case, BRD is often not a transient phenomenon.

The third set of studies comprises five longitudinal assessments of widows and widowers with and without BRD following spousal bereavement. These studies report high rates of depressive syndromes extending well beyond the first several months of bereavement. Overall, compared to non-bereaved controls, elevated rates of depression may last as long as 6 months (Bruce *et al*. 1990; Thompson *et al*. 1991), 9 months (Norris & Murrell, 1990), 18 months (Brent *et al*. 1994), 2 years (Harlow *et al*. 1991*b*; Stroebe & Stroebe, 1991; Zisook *et al*. 1993; Hays *et al*. 1994*a*, *b*; Carnelley *et al*. 1999; Turvey *et al*. 1999), 30 months (Gilewski *et al*. 1991), or even as long as 3 or more years (Bodnar & Kiecolt-Glaser, 1994; Mendes De Leon *et al*. 1994; Lichtenstein *et al*. 1996; Wilcox *et al*. 2003). Thus, depressive symptoms whose onset occurs within the post-bereavement window of time the DSM uses to exclude the diagnosis of MDE appears to be as chronic and/or recurrent as SMD.

Response to treatment

Also shown in Tables 1 and A7 are four open drug trials treating BRD (Jacobs *et al*. 1987; Pasternak *et al*. 1991; Zisook *et al*. 2001*a*, *b*; Oakley *et al*. 2002) and one placebo-controlled study, which included an arm of interpersonal psychotherapy (IPT) (Reynolds *et al*. 1999). All showed an effectiveness of antidepressants similar to response rates found in trials of SMD (AJP, 2000). In the only controlled study Reynolds *et al*. (1999) reported the highest rates of remission in the group receiving a combination of antidepressant medication and psychotherapy, closely mirroring that group's findings in similarly aged, non-bereaved cases with SMD.

Predictive validators in subjects within 2 months of bereavement

Each of the studies that assessed BRD at or within 2 months of bereavement found that BRD tends to persist over time (Clayton & Darvish, 1979; Lund *et al*. 1985; Harlow *et al*. 1991*b*; Thompson *et al*. 1991; Hays *et al*. 1994*b*; Karam, 1994; Zisook *et al*. 1997; Turvey *et al*. 1999), much like SMD. The only treatment study of individuals who the DSM would diagnose with 'bereavement' rather than MDD based on time since death also found BRD to respond to antidepressant medication similar to other studies of SMD (Zisook *et al*. 2001*b*).

DISCUSSION

This paper has reviewed data bearing on the similarities and differences between BRD and SMD. Studies assessing antecedent, concurrent and predictive validators were reviewed. Although none of the studies reviewed were designed specifically to examine whether BRD and SMD are different forms of the same disorder, the data presented do address this important question. We attempted to organize the available information to evaluate the following hypothesis: *BRD will resemble typical cases of SMD and therefore should be considered a form of SMD*. Table 2 summarizes the results of this empirical literature review from this perspective.

As might be expected given a range of methodological differences across the studies as well as the heterogeneity of MDD, results were not entirely consistent. However, a clear trend is noteworthy. The hypothesis receives considerably empirical support. From the perspective of multiple validators, BRD appears to be closely related to SMD. Like SMD, BRD is particularly frequent in bereaved individuals who are young,

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have past personal or family histories of SMD, and have poor social supports and compromised health. In addition, BRD has clinical characteristics reminiscent of SMD, including: impaired psychosocial functioning; co-morbidity with a number of anxiety disorders; and symptoms of worthlessness, psychomotor changes and suicidality. Moreover, symptoms of worthlessness, psychomotor changes and suicidality, mentioned in the DSM-TR as unlikely to occur in normal bereavement, can be long lasting and do not predict which individuals with BRD develop chronic or recurrent depression. BRD also has biological characteristics that reflect similarities with SMD: increased adrenocortical activity, impaired immune function and disrupted sleep architecture. Like SMD, BRD is common, long lasting and recurrent. Finally, BRD responds to antidepressant medication.

One can argue that BRD is not the same as SMD in that is often is mild, may remit spontaneously, is not self-perceived as an illness, and shares many symptoms in common with uncomplicated bereavement. But those features often characterize community samples of depressed individuals, as well (Brown *et al.* 1977; Solomon *et al.* 1997; Judd *et al.* 1999). The diagnosis of MDE may be difficult to make, especially soon after the death, as many symptoms of normal grief overlap with those of MDE. Nevertheless, such diagnostic challenges also are present in other instances of MDE.

We also tried to address, wherever the data allowed, whether the current bereavement exclusion for the diagnosis of MDD is consistent with empirical evidence. The 'bereavement exclusion' was instituted to prevent clinicians from diagnosing MDE when the individual was experiencing a 'normal' grief reaction. Recognizing that true MDEs could be triggered by the loss of a loved one, guidelines were proposed allowing a MDE to be diagnosed following the loss of a loved one if the duration exceeded 2 months and/or specific symptoms characteristic of a true MDE were present, particularly suicidal ideation, morbid preoccupation with worthlessness, and psychomotor retardation. Thus, the ideal study to test the validity of the bereavement exclusion would compare individuals with: (*a*) depressive syndromes beginning within 2 months of the loss of a loved one who do not have any of the above-mentioned symptoms with (*b*) MDEs of similar duration and symptom profile whose onset is unrelated to the death of a loved one. Unfortunately, we found no such studies in the literature.

Since the literature in this area is inconclusive, more research to address the validity of this important exclusion is necessary. If it is true that BRD is no different than SMD – and especially if BRD occurring within the first few months of the death of a loved one is no different than SMD – the bereavement exclusion for MDE may be invalid. This would in turn suggest that cases of MDD occurring after the loss of a loved one may be inappropriately dismissed as 'normal' grief reactions and therefore not treated. If the opposite is true, i.e. that the exclusion of MDD in the context of bereavement is valid, it raises questions about whether depression occurring after other losses (e.g. divorce, health, financial setbacks) are in need of diagnosis or treatment.

The DSM-IV-TR singles out bereavement as the only stressful life event that excludes the diagnosis of MDE when all other features are present. All substantial stressors, including the death of a loved, increase the risk for onset of a MDE (Brown *et al.* 1977; Lloyd, 1980; Kessler, 1997; Kendler *et al.* 2000). Kendler *et al.* (1995) has reported high rates of the onset of MDE following the death of a close relative (OR 16·0), and comparably high rates for several other stressful life events, such assault (OR 15·0), serious marital problems (OR 12·3) and divorce/break-up (OR 12·3). But in none of these cases, other than death of a loved one, does the presence of the stressor negate the diagnosis of MDE. If someone has met the criteria for MDE for more than 2 weeks shortly after they have been assaulted, divorced or suffered a myocardial infarct, we do not say they are not depressed and consider their reaction 'normal.' Rather, we make the diagnosis of MDE and consider the most appropriate treatment options (Popkin *et al.* 1985; Glassman *et al.* 2002).

Several caveats are important to note. First, the majority of studies reviewed here dealt with widowhood and include a preponderance of mid-life and older participants. Two of the studies involved children (losing parents) and adolescents (losing friends to suicide). More

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data on individuals throughout the lifespan and including a broader spectrum of types of bereavement would increase confidence in the generalizability of conclusions. Second, the primary source of studies included in this review was a Medline search followed by searching the bibliographies of identified manuscripts. Abstracts, posters, reviews and non-data-based chapters were not included. This method may not have captured all relevant articles. Third, some subjectivity may have influenced which studies were included and how some of the data may have been interpreted. Few of the available studies used structured interviews, and even fewer incorporated the most appropriate control groups to answer our key question. Finally, few studies used control groups ideally suited to test our hypothesis. With these caveats in mind, our conclusions must be interpreted with caution.

In summary, this review evaluated studies that bear on the similarities and differences between BRD and SMD. Although the definitive study has yet to be completed, the preponderance of available data supports the hypothesis that BRD resembles typical cases of SMD, and therefore, should be considered instances of SMD. The review also provides some support, although indirect and limited, that excluding recently bereaved individuals from the diagnosis of MDE, when all other symptomatic, duration and functional impairment criteria for MDE are met, may not be justified. BRD, as conceptualized in this review, is likely a mixture of cases including: those defined as 'Bereavement' by the DSM-IV; those that start out as DSM-IV 'Bereavement' and evolve into true MDEs; and others whose onset may precede the actual death of a loved one or be delayed for several months after the death. Although this review suggests that bereavement-associated depressive syndromes are probably similar to more typical depressions, the definitive work clarifying the relationship between 'normal grief' and MDE remains to be done. Given the highly heterogeneous nature of both BRD and SMD, the most propitious conclusion may be that, on average, these two syndromes appear to be closely related. Neither is a true 'natural kind', but with the rough kind of syndromal data available, these categories appear to be both examples of the same broad syndrome.

ACKNOWLEDGMENTS

The authors thank Jana Simmons and Ellen Solorzano for their help in literature searches and tabulating data and Drs Laura Dunn, Michael B. First, David Goldberg, Ronald Kessler, Barry Lebowitz, Jack Maser, John Rush, and Steven Shuchter for their thoughtful reviews and suggestions.

DECLARATION OF INTEREST

Dr Zisook is on the National Advisory Board of GSK, has received great support from PemLab and ASPECT, and honoraria from Glaxo SmithKline and Forest Laboratories.

NOTE

Supplementary information accompanies this paper on the Journal's website (http://journals.cambridge.org).

REFERENCES

AJP (2000). Practice guidelines for the treatment of patients with major depressive disorder (revision). *American Journal of Psychiatry* **157**, 23–30.

APA (1980). *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III). American Psychiatric Association: Washington, DC.

APA (2000). *Diagnostic and Statistical Manual of Mental Disorders* (4th edn, text revision). American Psychiatric Association: Washington, DC.

Barkow, K., Maier, W., Ustun, T. B., Gansicke, M., Wittchen, H. U. & Heun, R. (2002). Risk factors for new depressive episodes in primary health care: an international prospective 12-month follow-up study. *Psychological Medicine* **32**, 595–607.

Barry, L. C., Kasi, S. V. & Prigerson, H. G. (2002). Psychiatric disorders among bereaved persons. The role of perceived circumstances of death and preparedness for death. *American Journal of Geriatric Psychiatry* **10**, 447–457.

Bodnar, J. C. & Kiecolt-Glaser, J. K. (1994). Caregiver depression after bereavement: chronic stress isn't over when it's over. *Psychology and Aging* **9**, 372–380.

Boelen, P. A. & van den Bout, J. (2005). Complicated grief, depression and anxiety as distinct postloss syndromes: a confirmatory factor analysis study. *American Journal of Psychiatry* **162**, 2175–2177.

Bornstein, P. E., Clayton, P. J., Halikas, J. A., Maurice, W. L. & Robins, E. (1973). The depression of widowhood after thirteen months. *British Journal of Psychiatry* **122**, 561–566.

Brent, D. A., Perper, J., Mortiz, G., Allman, C., Liotus, L., Schweers, J., Roth, C., Balach, L. & Canobbio, R. (1993). Bereavement or depression? The impact of the loss of a friend to suicide. *Journal of the American Academy of Child and Adolescent Psychiatry* **32**, 1189–1199.

Brent, D. A., Peters, M. J. & Weller, E. (1994). Resolved: several weeks of depressive symptoms after exposure to a friend's suicide is 'major depressive disorder'. *Journal of the American Academy of Child and Adolescent Psychiatry* **33**, 582–586.

Briscoe, W. & Smith, J. B. (1975). Depression in bereavement and divorce. *Archives of General Psychiatry* **32**, 439–443.

https://doi.org/10.1017/S0033291707009865 Published online by Cambridge University Press

Brown, G. W., Harris, T. & Copeland, J. R. (1977). Depression and loss. *British Journal of Psychiatry* **130**, 1–18.

Bruce, M. L., Kim, K., Leaf, P. J. & Jacobs, S. (1990). Depressive episodes and dysphoria resulting from conjugal bereavement in a prospective community sample. *American Journal of Psychiatry* **145**, 608–611.

Byrne, G. J. A. & Raphael, B. (1997). The psychological symptoms of conjugal bereavement in elderly men over the first 13 months. *International Journal of Geriatric Psychiatry* **12**, 241–251.

Byrne, G. J. A. & Raphael, B. (1999). Depressive symptoms and depressive episodes in recently widowed older men. *International Psychogeriatrics* **11**, 67–74.

Carnelley, K. B., Wortman, C. B. & Kessler, R. C. (1999). The impact of widowhood on depression findings from a prospective survey. *Psychological Medicine* **29**, 1111–1123.

Carroll, B. J., Feinberg, M., Greden, J. F., Tarika, J., Albala, A. A., Haskett, R. F., James, N. M., Kronfol, Z., Lohr, N., Steiner, M., de Vigne, J. P. & Young, E. (1981). A specific laboratory test for the diagnosis of melancholia: standardization, validation, and clinical utility. *Archives of General Psychiatry* **38**, 15–22.

Clayton, P. J. (1974). Mortality and morbidity in the first year of widowhood. *Archives of General Psychiatry* **30**, 747–750.

Clayton, P. J. (1975). The effect of living alone on bereavement symptoms. *American Journal of Psychiatry* **132**, 133–137.

Clayton, P. J. & Darvish, H. S. (1979). Course of depressive symptoms following the stress of bereavement. In *Stress and Mental Disorders* (ed. J. E. Barrett), pp. 121–139. Raven Press: New York.

Clayton, P. J., Halikas, J. A. & Maurice, W. L. (1971). The bereavement of widowed. *Diseases of the Nervous System* **32**, 597–604.

Clayton, P. J., Halikas, J. A. & Maurice, W. L. (1972). The depression of widowhood. *British Journal of Psychiatry* **120**, 71–77.

Cole, M. G. & Dendukuri, N. (2003). Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *American Journal of Psychiatry* **160**, 1147–1156.

Dimond, M., Lund, D. A. & Caserta, M. S. (1987). The role of social support in the first two years of bereavement in an elderly sample. *Gerontologist* **27**, 599–604.

Dunn, A. J., Swiergiel, A. H. & de Beaurepaire, R. (2005). Cytokines as mediators of depression: what can we learn from animal studies? *Neuroscience and Biobehavioral Reviews* **29**, 891–909.

Freud, S. (1957). Mourning and melancholia. In *The Standard Edition of the Complete Psychological Works of Sigmund Freud, Volume XIV* (ed. James Strachey), pp. 237–258. The Hogarth Press: London.

Futterman, A., Gallagher, D., Thompson, L. W., Lovett, S. & Gilewski, M. (1990). Retrospective assessment of marital adjustment and depression during the first 2 years of spousal bereavement. *Psychology and Aging* **5**, 277–283.

Gallagher, E. G., Breckenridge, J. N., Thompson, L. W. & Peterson, J. A. (1983). Effects of bereavement on indicators of mental health in elderly widows and widowers. *Journal of Gerontology* **38**, 565–571.

Gaynes, B. N., Rush, A. J., Trivedi, M., Wisniewski, S. R., Balasubramani, G. K., Spencer, D. C., Peterson, T., Klinkman, M., Warden, D., Schneider, R. K., Castro, D. B. & Golden, R. N. (2005). A direct comparison of presenting characteristics of depressed outpatients from primary vs. specialty care settings: preliminary findings from the STAR*D clinical trial. *General Hospital Psychiatry* **27**, 87–96.

Gerra, G., Monti, D., Panerai, A. E., Sacerdote, P., Anderlini, R., Avanzini, P., Zaimovic, A., Brambilla, F. & Franceschi, C. (2003). Long-term immune-endocrine effects of bereavement: relationships with anxiety levels and mood. *Psychiatry Research* **121**, 145–158.

Gilewski, M. J., Farberow, N. L., Gallagher, D. E. & Thompson, L. W. (1991). Interaction of depression and bereavement on mental health in the elderly. *Psychology and Aging* **6**, 67–75.

Glassman, A. H., O'Connor, C. M., Califf, R. M., Swedberg, K., Schwartz, P., Bigger Jr., J. T., Krishnan, K. R., van Zyl, L. T., Swenson, J. R., Finkel, M. S., Landau, C., Shapiro, P. A., Pepine, C. J., Mardekian, J., Harrison, W. M., Barton, D., McIvor, M. & S.A.D.H.E.A.R.T. Group (2002). Sertraline treatment of major depression in patients with acute MI or unstable angina. *Journal of American Medical Association* **288**, 701–709.

Harlow, S. D., Goldberg, E. L. & Comstock, G. W. (1991*a*). A longitudinal study of risk factors for depressive symptomatology in the elderly widowed and married women. *American Journal of Epidemiology* **134**, 526–538.

Harlow, S. D., Goldberg, E. L. & Comstock, G. W. (1991*b*). A longitudinal study of the prevalence of depressive symptomatology in elderly widowed and married women. *Archives of General Psychiatry* **48**, 1065–1068.

Hays, J. C., Kasl, S. & Jacobs, S. (1994*a*). Past personal history of dysphoria, social support, and psychological distress following conjugal bereavement. *Journal of American Geriatric Society* **42**, 712–718.

Hays, J. C., Kasl, S. V. & Jacobs, S. C. (1994*b*). The course of psychological distress following threatened and actual conjugal bereavement. *Psychological Medicine* **24**, 917–927.

Horowitz, M. J., Siegel, B., Holen, A., Bonanno, G. A., Milbrath, C. & Stinson, C. H. (1997). Diagnostic criteria for complicated grief disorder. *American Journal of Psychiatry* **154**, 904–910.

Irwin, M., Daniels, M. & Weiner, H. (1987). Immune and neuroendocrine changes during bereavement. *Psychiatric Clinics of North America* **10**, 449–465.

Jacobs, S., Hansen, F., Berkman, L., Kasl, S. & Ostfeld, A. (1989). Depressions of bereavement. *Comprehensive Psychiatry* **30**, 218–224.

Jacobs, S., Nelson, J. C. & Zisook, S. (1987). Treating depressions of bereavement with antidepressants: a pilot study. *Psychiatric Clinics of North America* **10**, 501–510.

Judd, L. L., Akiskal, H. S., Zeller, P. J., Paulus, M., Leon, A. C., Maser, J. D., Endicott, J., Coryell, W., Kunovac, J. L., Mueller, T. I., Rice, J. P. & Keller, M. B. (2000). Psychosocial disability during the long-term course of unipolar major depressive disorder. *Archives of General Psychiatry* **57**, 375–380.

Judd, L. L., Paulus, M. P. & Zeller, P. (1999). The role of residual subthreshold depressive symptoms in early episode relapse in unipolar major depressive disorder. *Archives of General Psychiatry* **56**, 764–765.

Karam, E. G. (1994). The nosological status of bereavement-related depressions. *British Journal of Psychiatry* **165**, 48–52.

Kendler, K. S. (1980). The nosologic validity of paranoia (simple delusional disorder): a review. *Archives of General Psychiatry* **37**, 699–706.

Kendler, K. S. (1999). Casual relationship between stressful life events and the onset of major depression. *American Journal of Psychiatry* **156**, 837–841.

Kendler, K. S., Kessler, R. C., Walters, E. E., MacLean, C., Neale, M. C., Heath, A. C. & Eaves, L. J. (1995). Stressful life events, genetic liability, and onset of an episode of major depression in women. *American Journal of Psychiatry* **152**, 833–842.

Kendler, K. S., Thornton, L. M. & Gardner, C. O. (2000). Stressful life events and previous episodes in the Etiology of major depression in women: an evaluation of the 'Kindling' hypothesis. *American Journal of Psychiatry* **157**, 1243–1251.

Kessler, R. (1997). The effects of stressful life events on depression. *Annual Review of Psychology* **48**, 191–214.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R. & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* **62**, 593–602.

Kosten, T. R., Jacobs, S. & Mason, J. W. (1984). The dexamethasone suppression test during bereavement. *Journal of Nervous and Mental Disease* **172**, 359–360.

Kraepelin, E. (1899/1990). *Psychiatry: A Textbook for Students and Physicians* (6th edn). Science History Publications: Canton, MA.

https://doi.org/10.1017/S0033291707009865 Published online by Cambridge University Press

Kupfer, D. J., Ehlers, C. L., Frank, E., Grochocinski, V. J. & McEachran, A. B. (1991). EEG sleep profiles and recurrent depression. *Biological Psychiatry* **30**, 641–655.

Lesch, K. P., Laux, G., Schulte, H. M., Pfuller, H. & Beckmann, H. (1988). Corticotropin and cortisol response to human CRH as a probe for HPA system integrity in major depressive disorder. *Psychiatry Research* **24**, 25–34.

Lewinsohn, P. M., Hoberman, H. M. & Rosenbaum, M. (1988). A prospective study of risk factors for unipolar depression. *Journal of Abnormal Psychology* **97**, 251–264.

Lichtenstein, P., Gatz, M., Pedersen, N. L., Berg, S. & McClearn, G. E. (1996). A co-twin-control study of response to widowhood. *Journal of Gerontology: Psychological Sciences* **51B**, 279–289.

Linn, M. W., Linn, B. S. & Jensen, J. (1984). Stressful events, dysphoric mood, and immune responsiveness. *Psychological Reports* **54**, 219–222.

Lichtenthal, W. G., Cruess, D. G. & Prigerson, H. G. (2004). A case for establishing complicated grief as a distinct mental disorder in DSM-V. *Clinical Psychology Review* **24**, 637–662.

Lloyd, C. (1980). Life events and depressive disorder reviewed. *Archives of General Psychiatry* **37**, 541–548.

Lund, D. A., Caserta, M. S. & Dimond, M. F. (1986). Gender differences through two years of bereavement among the elderly. *Gerontologist* **26**, 314–320.

Lund, D. A., Dimond, M. F., Caserta, M. S., Johnson, R. J., Poulton, J. L. & Connelly, J. R. (1985). Identifying elderly with coping difficulties after two years of bereavement. *Omega* **16**, 213–223.

McHorney, C. A. & Mor, V. (1988). Predictors of bereavement depression and its health services consequences. *Medical Care* **26**, 882–893.

Mendes De Leon, C. F., Kasl, S. V. & Jacobs, S. (1994). A prospective study of widowhood and changes in symptoms of depression in a community sample of the elderly. *Psychological Medicine* **24**, 613–624.

Nemeroff, C. B. (1998). The neurobiology of depression. *Scientific American* **278**, 42–49.

Norris, F. H. & Murrell, S. A. (1990). Social support, life events, and stress as modifiers of adjustment to bereavement by older adults. *Psychology and Aging* **5**, 429–436.

Nuss, S. & Zubenko, G. S. (1992). Correlates of persistent depressive symptoms in widows. *American Journal of Psychiatry* **149**, 346–351.

O'Connor, M., Allen, J. J. B. & Kaszniak, A. W. (2002). Autonomic and emotion regulation in bereavement and depression. *Journal of Psychosomatic Research* **52**, 183–185.

Oakley, F., Khin, N. A., Parks, R., Bauer, L. & Sunderland, T. (2002). Improvement in activities of daily living in elderly following treatment for post-bereavement depression. *Acta Psychiatrica Scandinavica* **105**, 231–234.

Onrust, S. A. & Cuijpers, P. (2006). Mood and anxiety disorders in widowhood: a systematic review. *Aging and Mental Health* **10**, 327–334.

Pasternak, R. E., Reynolds, C. R. R., Schlernitzauer, M., Hoch, C. C., Buysse, D. J., Houck, P. R. & Perel, J. M. (1991). Acute open-trial nortriptyline therapy of bereavement-related depression in late life. *Journal of Clinical Psychiatry* **52**, 307–310.

Popkin, M. K., Callies, A. L. & Mackenzie, T. B. (1985). The outcome of antidepressant use in the medically ill. *Archives of General Psychiatry* **42**, 1160–1163.

Prigerson, H. G., Bierhals, A. J., Kasi, S. V., Reynolds, C. F., Shear, M. K., Day, N., Beery, L. C., Newsom, J. T. & Jacobs, S. (1997). Traumatic grief as a risk factor for mental and physical morbidity. *American Journal of Psychiatry* **154**, 616–623.

Prigerson, H. G., Bierhals, A. J., Kasl, S. V., Reynolds 3rd, C. F., Shear, M. K., Newsom, J. T. & Jacobs, S. (1996). Complicated grief as a disorder distinct from bereavement-related depression and anxiety: a replication study. *American Journal of Psychiatry* **153**, 1484–1486.

Rechlin, T., Weis, M. & Claus, D. (1994). Heart rate variability in depressed patients and differential effects of paroxetine and amitriptyline on cardiovascular autonomic functions. *Pharmacopsychiatry* **27**, 124–128.

Reynolds, C. F., Hoch, C. C., Buysse, D. J., Houck, P. R., Schlernitzauer, M., Frank, E., Mazumdar, S. & Kupfer, D. J. (1992). Electroencephalographic sleep in spousal bereavement and bereavement-related depression of late life. *Biological Psychiatry* **31**, 69–82.

Reynolds, C. F. & Kupfer, D. J. (1987). Sleep research in affective illness: state of the art circa 1987. *Sleep* **10**, 199–215.

Reynolds, C. F., Miller, M. D., Pasternak, R. E., Frank, E., Perel, J. M., Cornes, C., Houck, P. R., Mazumdar, S., Dew, M. A. & Kupfer, D. J. (1999). Treatment of bereavement-related major depressive episodes in later life: a controlled study of acute and continuation treatment with nortriptyline and interpersonal therapy. *American Journal of Psychiatry* **156**, 202–208.

Richards, J. G. & McCallum, J. (1979). Bereavement in the elderly. *New Zealand Medical Journal* **89**, 201–204.

Robins, E. & Guze, S. B. (1970). Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *American Journal of Psychiatry* **126**, 983–987.

Roy, A., Gallucci, W., Avgerinos, P., Linnoila, M. & Gold, P. (1988). The CRH stimulation test in bereaved subjects with and without accompanying depression. *Psychiatry Research* **25**, 145–156.

Schleifer, S. J., Keller, S. E., Meyerson, A. T., Raskin, M. J., Davis, K. L. & Stein, M. (1984). Lymphocyte function in major depressive disorder. *Archives of General Psychiatry* **41**, 484–486.

Shear, K., Frank, E., Houck, P. R. & Reynolds, C. F. (2005). Treatment of complicated grief: a randomized controlled trial. *Journal of the American Medical Association* **293**, 2601–2608.

Shuchter, S. R. (1986). In *Dimensions of Grief: Adjusting to the Death of a Spouse*. Jossey-Bass: San Francisco.

Shuchter, S. R., Zisook, S., Kirkorowicz, C. & Risch, C. (1986). The dexamethasone suppression test in acute grief. *American Journal of Psychiatry* **143**, 879–881.

Silverman, G. K., Johnson, J. G. & Prigerson, H. G. (2001). Preliminary explorations of the effects of prior trauma and loss on risk for psychiatric disorders in recently widowed people. *Israel Journal of Psychiatry and Related Sciences* **38**, 202–215.

Sokero, T. P., Melartin, T. K., Rytsala, H. J., Leskela, U. S., Lestela-Mielonen, P. S. & Isometsa, E. T. (2005). Prospective study of risk factors for attempted suicide among patients with DSM-IV major depressive disorder. *British Journal of Psychiatry* **186**, 314–318.

Solomon, D. A., Keller, M. B., Leon, A. C., Mueller, T. I., Shea, M. T., Warshaw, M., Maser, J. D., Coryell, W. & Endicott, J. (1997). Recovery from major depression. A 10-year prospective follow-up across multiple episodes. *Archives of General Psychiatry* **54**, 1001–1006.

Stroebe, M. & Stroebe, W. (1991). Does 'grief work' work? *Journal of Consulting and Clinical Psychology* **59**, 479–482.

Thompson, L. W., Gallagher-Thompson, D., Futterman, A., Gilewski, M. J. & Peterson, J. (1991). The effects of late-life spousal bereavement over 30-month interval. *Psychology and Aging* **6**, 434–441.

Turvey, L. C., Carney, C., Arndt, S., Wallace, R. B. & Herzog, R. (1999). Conjugal loss and syndromal depression in a sample of elders aged 70 years and older. *American Journal of Psychiatry* **156**, 1596–1601.

Weissman, M. M., Wickramaratne, P., Nomura, Y., Warner, V., Verdeli, H., Pilowsky, D. J., Grillon, C. & Bruder, G. (2005). Families at high and low risk for depression: a 3-generation study. *Archives of General Psychiatry* **62**, 29–36.

Weller, E. B., Weller, R. A., Fristad, M. A. & Bowes, J. M. (1990). Dexamethasone suppression test and depressive symptoms in bereaved children: a preliminary report. *Journal of Neuropsychiatry and Clinical Neurosciences* **2**, 418–421.

Weller, R. A., Weller, E. B., Fristad, M. A. & Bowes, J. M. (1991). Depression in recently bereaved prepubertal children. *American Journal of Psychiatry* **148**, 1536–1540.

Wilcox, S., Evenson, K. R., Aragaki, A., Wassertheil-Smoller, S., Mouton, C. P. E. & Loevinger, B. L. (2003). The effects of

https://doi.org/10.1017/S0033291707009865 Published online by Cambridge University Press

widowhood on physical and mental health, health behaviors, and health outcomes: The women's' health initiative. *Health Psychology* **22**, 513–522.

Zisook, S., Paulus, M., Shuchter, S. R. & Judd, L. L. (1997). The many faces of depression following spousal bereavement. *Journal of Affective Disorders* **45**, 85–95.

Zisook, S. & Shuchter, S. R. (1991*a*). Early psychological reaction to the stress of widowhood. *Psychiatry* **54**, 320–333.

Zisook, S. & Shuchter, S. R. (1991*b*). Depression throughout the first year after the death of a spouse. *American Journal of Psychiatry* **148**, 1346–1352.

Zisook, S. & Shuchter, S. R. (1993*a*). Major depression associated with widowhood. *American Journal of Geriatric Psychiatry* **1**, 316–326.

Zisook, S. & Shuchter, S. R. (1993*b*). Uncomplicated bereavement. *Journal of Clinical Psychiatry* **54**, 365–372.

Zisook, S., Shuchter, S. & Dunn, L. B. (2001*a*). Grief and depression: diagnostic and treatment challenges. *Primary Psychiatry* **8**, 37–38, 51–53.

Zisook, S., Shuchter, S. R., Pedrelli, P., Sable, J. & Deaciuc, S. C. (2001*b*). Bupropion sustained release for bereavement: results of an open trial. *Journal of Clinical Psychiatry* **62**, 227–230.

Zisook, S., Shuchter, S. R., Sledge, P. & Mulvihill, M. (1993). Aging and bereavement. *Journal of Geriatric Psychiatry and Neurology* **6**, 137–143.

Zisook, S., Shuchter, S. R., Sledge, P. A., Paulus, M. & Judd, L. L. (1994). The spectrum of depressive phenomena after spousal bereavement. *Journal of Clinical Psychiatry* **55** (Suppl.), 29–36.

https://doi.org/10.1017/S0033291707009865 Published online by Cambridge University Press