

Original contribution

Stressful life events, personal losses, and perimenopause-related depression

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Summary

We compared the number and quality of life events reported by depressed perimenopausal women and a non-depressed comparison group. Additionally, we examined the effects of the presence of hot flushes on life event reports. All women were 44–55 years old, had irregular menses and elevated plasma gonadotropin levels. The Psychiatric Epidemiology Research Interview recorded both the frequency of occurrence and the desirability of life events experienced by the women during the six months prior to the interview. Depressed perimenopausal women ($n = 50$) reported significantly more undesirable events [Student's t -test (unpaired) with Bonferroni correction, $t_{98} = 3.9$, $p = 0.001$] but not more exit events (e.g., divorce, last child leaving home or death in family) ($t_{98} = 0.9$, $p = \text{NS}$) compared to the non-depressed women ($n = 50$). There were no effects of hot flushes on these diagnostic differences. The “empty nest” syndrome does not appear to be relevant in the development of perimenopausal depression. Nevertheless, independent of the presence of hot flushes, perimenopausal depressed women are more likely to report both negative life events and diminished self esteem.

Keywords: Depression; perimenopause; life events; midlife.

Introduction

Depressions occurring coincident with the menopausal transition or perimenopause have generated considerable controversy, exemplified by the now century old argument about whether “involutional depressions” in general, or perimenopausal depressions in particular, are in any way distinct from depressions occurring at other points in the life cycle. A relationship between stressful life events and both major and subsyndromal depressions has been documented, with life events

reported to be especially relevant to first onset depressions compared to recurrent depressions (Ormel et al., 2001; Kendler et al., 2000; Ezquiaga et al., 1987). Additionally, several factors, including genetic predisposition (Caspi et al., 2003) and personality traits (i.e., self efficacy (Maciejewski et al., 2000)), are important mediators of the differential effects of negative life events on the course of a depressive illness. Some, but not all, studies suggested that the perimenopause and midlife are associated with the occurrence of substantially more negative life events compared to other stages of a woman's life. For example, Greene and Cook (1980) reported that perimenopausal women reported more negative life events than younger women. Additionally, the observed increase in negative life events predominantly reflected the occurrence of events related to interpersonal losses (e.g., children leaving the home, death of parents) consistent with the construct of the empty nest syndrome. In contrast to Greene and Cook, Dennerstein (2001) observed that empty nest-types of events were neither confined to midlife nor were they necessarily associated with negative mood (in fact these were more typically associated with positive mood states). Nonetheless, both Greene and Cook and Dennerstein found that the presence of negative life events was associated with perimenopausal mood and behavioral symptoms. In fact, Greene and Cook suggested that negative life events may be causally related to the onset of depression during the

perimenopause. No studies to date have attempted to systematically determine whether the frequency or impact of life events distinguish women who develop depression in the context of the perimenopause from those who do not. In this study we examined the number and quality of life events reported by depressed perimenopausal women and non-depressed controls with and without self-reported hot flashes. All women had the presence or absence of depression confirmed by a standardized diagnostic interview and had hormonal evidence of the perimenopause.

Methods

Subject selection

Prior to selection all women participated in an eight week screening phase consisting of four clinic visits at two week intervals during which mood ratings were completed and blood samples were obtained to measure plasma levels of follicle stimulating hormone (FSH). All women reported menstrual cycle irregularity of at least six months duration but not more than one year of amenorrhea. Additionally, all women met perimenopausal endocrine criteria as follows: plasma levels of FSH ≥ 14 IU/L (performed at NIH Clinical Center Pathology Department) on three of four screening visits. Plasma FSH levels of 14 IU/L represent approximately two standard deviations above the mean value for early follicular phase FSH levels in women between the ages of 25 and 35 (consistent with criteria for defining the perimenopause suggested by the Stages of Reproduction Aging Workshop [STRAW criteria] (Soules et al., 2001)). At each clinic visit all subjects completed the Center for Epidemiologic Studies – Depression (CES-D) Scale (Radloff, 1977) and the Beck Depression Inventory (BDI) (Beck et al., 1961). A modified Daily Rating Form (DRF) (Halbreich et al., 1982) was completed, which rated the severity of several mood and behavioral symptoms as well as day and night time hot flashes. The DRF rates the severity of a symptom on a six point scale ranging from 1 (not at all) to 6 (extreme). The presence of hot flashes was operationally defined by a mean score of >2 on the DRF (2 = minimal) during the eight week baseline. Subjects were instructed to use the severity scale as a composite of their hot flush frequency and severity. All subjects who were married or who reported being involved in a significant relationship completed a Marital Adjustment Scale evaluating the quality and level of satisfaction with their current relationship: scores of 100 or less on this scale indicate maladjustment in the marital relationship (Locke and Wallace, 1959).

Women were excluded if they had a medical illness (determined by history, physical exam, and routine laboratory testing including thyroid function tests).

Patients were 50 women between the ages of 44 and 55 years who presented to the NIMH midlife clinic with a history of onset of depression in association with menstrual cycle irregularity and who met study diagnostic criteria for perimenopause-related depression. All women were referred by their personal physicians or responded to advertisements in local newspapers.

In addition to meeting perimenopausal endocrine criteria, perimenopausal depression was defined as follows:

- 1) self report of the onset of depression associated with menstrual cycle irregularity,
- 2) the diagnosis of major or minor depression determined by a structured diagnostic interview, the Structured Clinical Interview for DSM-III (Spitzer et al., 1990) (supplemented by a portion of the Schedule for Affective Disorders and Schizophrenia – Lifetime Version (Spitzer and Endicott, 1979) assessing the presence of both minor and atypical depressive illnesses), and
- 3) scores on the Center for Epidemiologic Studies – Depression Scale ≥ 10 (Radloff, 1977) during three out of the four screening visits.

Women were excluded if they had a history of psychiatric illness during the two years prior to the reported onset of their current episode of depression. After completing the evaluation (above), the Modified Life Events Section of the Psychiatric Epidemiologic Research Interview (PERI-M) (Dohrenwend et al., 1978) was administered to those women who met criteria for perimenopause-related depression. Depressed women (regardless of whether they met study criteria) were referred for standard antidepressant treatment or in those women meeting criteria for perimenopause-related depression offered the option to participate in a double-blind, placebo-controlled trial of estradiol in perimenopausal depression.

Controls were 50 non-depressed perimenopausal women recruited separately from the depressed women through advertisements in the hospital newsletter. The non-depressed, healthy, medication-free controls participated in a similar screening program and met the same clinical (i.e., age, menstrual cycle history) and laboratory requirements as the depressed perimenopausal women, with the exception of the absence of complaints of mood symptoms, confirmed by the administration of the structured diagnostic interview and standardized mood rating scales (described above). Controls were excluded if they had any current or recent (two years prior to the study) Axis I psychiatric condition. Controls received remuneration for their participation in the study as determined by the guidelines of the NIH Office of Normal Volunteers. The protocol was approved by the NIMH Intramural Research Review Subpanel, and written informed consent was obtained from all subjects.

Group assignment

Subjects were recruited from consecutive admissions to complete sample sizes of 50 subjects per group. The one hundred participants were assigned to one of four groups according to the presence or absence of a depressive syndrome (major or minor depression) and, within each diagnostic group, by self-ratings of hot flush symptomatology (average DRF score >2 (present) or ≤ 2 (absent)).

Life events interview

The PERI-M (Dohrenwend et al., 1978) is a structured interview that documents both the frequency of occurrence and the desirability of life events experienced by the respondent as well as by

other persons identified as important to the respondent during the six months prior to the time of interview. The interview inquires about 110 life events in the following 11 categories: school, work, love, health, crime and legal, money and financial, child-birth-related, family and household, residence, personal, and death. The desirability scale ranges from 1 = extremely negative to 7 = extremely positive. Scores of 1 or 2 are rated as negative; scores of 3, 4 or 5 are rated as neutral; scores of 6 or 7 are rated as positive. Exit events defined as “real or perceived loss of a personally relevant object” (e.g., death of a loved one, last child leaving home, divorce, loss of a job) are found in several categories and are combined into the total exit score. Additionally, items number 82–86 reflect events in which somebody left the respondent’s household and, therefore, were grouped together as “empty nest” events. The interview obtains the following additional measures:

- 1) counts of events, consisting of both the total number of events (to any person identified or to the respondent only) and the total number of events in each of 11 categories (listed above) (to any person identified or to the respondent only);
- 2) subjective measures, consisting of the number of events rated by the respondent as having at least a moderately negative effect on her life (occurring to any person identified or the respondent only) and the number of events that were unanticipated, out of the respondent’s control, or negatively impacted on the person’s self esteem; and
- 3) component measures of the Peri-M, including the following: Holmes-Rahe simulated and modified scores (distinguished by the additional weights assigned to recurrent events in the modified scores (Holmes and Rahe, 1967)), Tennant measures of stress and distress (Tennant and Andrews, 1976), and Paykel measure of distress (Paykel et al., 1971; Paykel, 2001).

Statistical analysis

In the primary analyses differences in the counts of the total number of life events, the number of negative life events, the number of exit events, and the number of “empty nest” events were compared by Student’s t-test (unpaired, 2-tailed) across diagnostic groups. Additionally, we examined differences in the life events impacting negatively on self-esteem or over which the respondent felt no control or which were unanticipated. In these seven primary analyses, a Bonferroni adjustment of the p values was performed due to the multiple ($n = 7$) comparisons. Secondary comparisons examined diagnostic differences with unpaired Student’s t-test and the corresponding Bonferroni adjustments in the component measures of the Peri-M (e.g., Holmes-Rahe) and the number of life events in each of the 11 categories. Differences between depressed and non-depressed women in measures of age, mood rating scores (BDI and CES-D), Marital Adjustment Scores, plasma FSH levels (average of the four values obtained at screening), ethnicity, years of education, and marital and employment status were compared with Chi square (or Fisher exact) or Student’s t-test when appropriate. Finally, to examine potential effects of hot flushes in life events reports, PERI-M variables (compared in the primary analyses) were compared by analysis of variance (ANOVA), with diagnostic group (depressed versus non-depressed) and presence or absence of hot flushes as the between subjects variables.

Chi square analysis was employed to evaluate differences between groups in a past history of major depression. Student’s t-test was employed in the depressed women to evaluate whether the presence or absence of a past history of major depression differentially influenced the following measures: the number of negative and exit life events, the number of life events that impacted negatively on self esteem, events considered out of the subject’s control, and events that were unanticipated. Additionally, to avoid the possibility that a past history of major depression in some subjects may confound the observed diagnosis-related effects on life events, we compared the counts of life events in subgroups of perimenopausal depressed ($n = 41$) and non-depressed women ($n = 49$) with no past history of major depression. Correlations between mood ratings and the reported number of undesirable life events were analyzed by Pearson correlation coefficients. Data are reported as mean \pm SD in text and tables. Unless otherwise stated, all t values are Bonferroni corrected.

Results

Subject characteristics (Table 1)

Eleven of the 50 depressed women met criteria for major depression; the remainder met criteria for minor depression. No significant differences in age and age of onset or duration of menstrual cycle irregularity were observed between depressed and non-depressed women. Depressed women did not differ from controls in measures of ethnicity (Caucasian versus non-Caucasian – principally African American), years of education, marital status, employment status, and socio-economic class (all subjects lived in suburban Maryland). Additionally, all subjects reported comparable numbers of important persons in their daily social network (9.6 ± 4.2 and 10.5 ± 5.9 persons, respectively [$t_{98} = 0.9$, $p = \text{NS}$]), a proxy for social support (Murrell et al., 1991).

When we compared the total number of past depressive episodes (major and minor), no differences were observed between depressed and non-depressed women. Seventy-five of the subjects (37 depressed and 38 non-depressed) were married or reported a significant partner relationship, and these women completed the Marital Adjustment Scale. The depressed women reported significantly lower marital satisfaction compared to the non-depressed women: 23 depressed women compared with 10 non-depressed women scored ≤ 100 (Chi square = 9.8, $p < 0.01$).

Life event scale scores

Primary comparisons

Depressed perimenopausal women reported significantly more life events of all types compared to the non-depressed women (uncorrected $t_{98} = 2.3$, $p = 0.02$).

Table 1. Subject characteristics in women (n = 50) with and without (n = 50) perimenopause-related depression

Variable	Depressed women mean (SD)	Non-depressed women mean (SD)	Statistical comparison
Age (years)	48.6 (3.5)	49.2 (3.2)	$t_{98} = 0.9$ (NS)
Education (years)**	15.5 (2.0)	16.0 (2.0)	$t_{91} = 1.2$ (NS)
Duration of menstrual cycle irregularity (months)	24.9 (18.3)	28.5 (25.4)	$t_{98} = 0.8$ (NS)
Plasma FSH (IU/L)	66.5 (35.3)	70.4 (51.7)	$t_{98} = 0.5$ (NS)
BDI scores	13.2 (6.8)	3.6 (2.8)	$t_{98} = 9.3$ ($p < 0.001$)
CES-D scores	21.7 (8.2)	6.1 (3.6)	$t_{98} = 10.8$ ($p < 0.001$)
Marital Adjustment Scale scores	87.7 (30.5)	112.5 (21.5)	$t_{73} = 4.1$ ($p < 0.001$)
No. married (% married)	37 (74%)	38 (76%)	Chi square = 0.1 (NS)
No. employed (% employed)	42 (84)	44 (88)	Chi square = .3 (NS)
Ethnicity (% Caucasian)	47 (94)	43 (86)	Fisher Exact (NS)
No. with past minor depression	16	17	Fisher Exact (NS)
No. with past major depression	9	1	Fisher Exact (0.02)

** These data were missing in seven women.

However, when a Bonferroni correction for the seven primary comparisons was performed, the diagnosis-related differences in total events were no longer significant (Table 2). The depressed perimenopausal women reported a significantly increased number of undesirable (negative) events compared to the non-depressed women ($t_{98} = 3.9$, $p = 0.001$), but there were no significant differences in the number of life events viewed as positive ($t_{98} = 0.7$, $p = \text{NS}$) or neutral ($t_{98} = 0.07$, $p = \text{NS}$). Depressed women also showed a significantly increased proportion of negative events and a decreased proportion

of neutral events compared to non-depressed women (Table 2). Depressed women did not report an increased number of either exit or “empty nest” events compared to controls ($t_{98} = 0.9$ and 0.2 , respectively, $p = \text{NS}$). Finally, compared to non-depressed women, depressed women reported significantly greater numbers of life events that decreased their self-esteem ($t_{98} = 4.1$, $p < 0.001$), that were not anticipated ($t_{98} = 3.6$, $p = 0.003$), and that were felt to be out of the responder’s control ($t_{98} = 3.8$, $p = 0.001$) (Bonferroni adjusted for seven comparisons).

Table 2. Number (#) of life events in women with perimenopause-related depression (n = 50) and a non-depressed perimenopausal comparison group (n = 50)

Life events variables	Depressed women mean (SD)	Non-depressed women mean (SD)	Student’s t-test [2 groups t_{98} (p)]
Total # of events	12.3 (7.1)	9.4 (5.3)	2.3 (NS) ^b
Exit events	1.1 (1.5)	0.8 (1.0)	0.9 (NS) ^b
Empty nest events	0.24 (0.43)	0.26 (0.66)	0.2 (NS) ^b
Undesirable events	4.9 (3.4)	2.6 (2.6)	3.9 (0.001) ^b
Decreased self-esteem	1.4 (1.9)	0.2 (0.5)	4.1 (<0.001) ^b
Unanticipated	2.4 (2.1)	1.2 (1.1)	3.6 (0.003) ^b
Uncontrollable	2.4 (1.9)	1.2 (1.1)	3.8 (0.001) ^b
Percent rated undesirable ^a	42.4 (23.5)	25.7 (21.8)	3.7 (<0.001)
Percent rated desirable ^a	35.6 (20.5)	41.0 (24.0)	1.1 (NS)
Percent rated neutral ^a	22.0 (17.0)	34.0 (25.2)	2.8 (0.007)
Holmes-Rahe	137.3 (80.6)	88.5 (60.0)	3.4 (0.001) ^c
Holmes-Rahe (modified)	164.3 (96.1)	97.2 (68.3)	4.0 (<0.001) ^c
Tennant-distress	48.0 (35.1)	30.0 (21.8)	3.1 (0.003) ^c
Tennant-stress	63.4 (42.1)	47.2 (31.4)	2.2 (0.03) ^c
Paykel	40.0 (27.4)	28.3 (17.6)	2.5 (0.01) ^c

Values represent the average number of events (or the average score in the derived scales) occurring in subjects during the previous six months.

^a Percent of total number of events reported that were rated undesirable, desirable, and neutral.

^b Bonferroni adjusted for seven comparisons.

^c Bonferroni adjusted for five comparisons.

Table 3. Number of life events by category in women with (n = 50) and without (n = 50) perimenopause-related depression

Life events variables	Depressed women mean (SD)	Non-depressed women mean (SD)	Student's t-test (unpaired)*
School	0.8 (0.9)	0.8 (0.9)	0.2 (NS)
Work	2.7 (1.8)	2.3 (1.6)	1.2 (NS)
Love	1.4 (1.7)	1.0 (1.2)	1.6 (NS)
Health	2.7 (2.2)	1.6 (1.5)	3.0 (<0.05)
Legal	0.4 (0.6)	0.3 (0.6)	0.2 (NS)
Money	1.7 (1.7)	1.1 (1.1)	1.9 (NS)
Birth	0.3 (0.6)	0.2 (0.6)	0.5 (NS)
Household	0.5 (0.7)	0.5 (0.9)	0.1 (NS)
Residence	0.1 (0.3)	0.1 (0.4)	0.6 (NS)
Personal	1.3 (1.2)	1.2 (1.0)	0.5 (NS)
Death	0.3 (0.6)	0.2 (0.4)	0.9 (NS)

Values represent the average number of events occurring in each subject during the previous six months.

* p values adjusted for 11 comparisons.

Additional comparisons

Similar diagnosis-related differences were observed in the component measures, with depressed perimenopausal women reporting significantly more negative events and/or stress compared to the controls: Holmes-Rahe score ($t_{98} = 3.4$, $p < 0.001$), Holmes-Rahe modified score ($t_{98} = 4.0$, $p < 0.001$), Tennant distress and stress scores ($t_{98} = 3.1$, and 2.2 , $p = 0.003$ and $p = 0.03$, respectively), and Paykel score ($t_{98} = 2.5$, $p = 0.01$) (adjusted for five comparisons) (Table 2).

There were no significant diagnostic differences in the eleven individual life event categories (Table 3), with the exception of health-related events: depressed women described these events as occurring more frequently than the non-depressed women.

No significant correlation was present between the BDI or CES-D scores and the number of undesirable events in depressed women ($r = 0.1-0.2$, $p = \text{NS}$). The increased number of undesirable events ($t_{98} = 3.3$, $p < 0.01$) and the number of events negatively impacting on self-esteem ($t_{98} = 4.1$, $p < 0.001$) in depressed women also were observed when women with a past history of depression were excluded from the analysis. Similarly, depressed women with a past history of depression (i.e., recurrent depression) did not report more undesirable events than those with no past history (first onset depression) ($t_{98} = 0.8$, $p = \text{NS}$).

Finally, there were no significant main or interaction effects of hot flushes observed in any of the comparisons of Peri-M variables.

Discussion

In this study we asked two questions about the relationship between life events and perimenopausal depression.

First, do women with perimenopausal depression report a greater number of personal losses than non-depressed perimenopausal women? Second, are the reports by women with perimenopausal depression of personal losses/exit or negative events influenced by the co-occurrence of hot flushes? Some studies suggest that the perimenopause is associated with the occurrence of a larger number of negative life events compared to other stages of life. Greene and Cooke (Greene and Cooke, 1980; Cooke and Greene, 1981; Greene, 1983) described an increased frequency of negative events reported by women during the early perimenopause, especially between ages 40 and 44 years. The observed increase in stressful events reflected an increase in personal losses or exit events (Cooke and Greene, 1981). Additionally, psychological symptoms in the climacteric women correlated with the number of exit events (Cooke and Greene, 1981; Greene and Cooke, 1980). Based on these latter observations, perimenopausal depression was suggested to occur secondary to an increase in exit events, comparable to the empty nest syndrome. Greene (1983) also suggested that climacteric women were more vulnerable to experience stress-induced negative mood symptoms. In contrast, Veeninga (1989) reported that women attending a menopause clinic did not report an increased number of negative events or exit events compared with a non-symptomatic outpatient comparison group. Menopause-clinic attendees, however, did report an increase in the negative impact of events compared to controls. Thus, both Veeninga and Greene suggested that perimenopausal depressed women were distinguished from non-depressed women by their greater vulnerability to the negative effects of life events on self esteem. Similar suggestions were made by Ballinger (1985), who observed that perimenopausal women with depressive symptoms reported a greater

negative impact of life events and more feelings of being stressed than a group of asymptomatic controls. More recently, Dennerstein et al. (2001) reported that stressful life events did, in fact, impact negatively on the mood of women during the transition through menopause. However, she also observed that the empty nest syndrome resulted in a positive mood as frequently if not more often than it did a negative mood in middle-aged women (Dennerstein et al., 2002). We failed to observe significant differences in either the number of personal losses or exit events reported by depressed perimenopausal women compared to controls and could not, therefore, confirm the findings of Greene and Cooke. Our subjects were in the late perimenopause and, therefore, older than those reported on by Greene and Cooke (Cooke and Greene, 1981). Nonetheless, similar findings to ours were obtained by Chou et al. (2000) in a sample of elderly Chinese men and women. Thus, we were unable to confirm the relevance of an increased number of exit or personal loss events (or the “empty nest syndrome”) in depressed perimenopausal women.

In contrast to the similarities between depressed women and control subjects in reported exit events and personal losses, depressed perimenopausal women were distinguished from controls by their reports of significantly more negative life events, and this difference was also observed in the component life events scales. Not only were more negative life events reported to have occurred in depressed women compared to controls, but as well, they reported more life events that negatively impacted on their self esteem, were considered uncontrollable, and were unanticipated. These findings are similar to those reported by both Veeninga et al. (1989) and Ballinger (1985) and suggest that both an increased number of negative life events and a greater negative impact of events, but not more personal losses or exit events, characterize perimenopausal depression. The number and quality of life events recorded in this study reflected each woman’s self-report and hence her perception of the event; events were not independently characterized. The greater number of negative life events reported by depressed women compared to controls could reflect an actual difference in the number of events occurring in these women’s lives. Alternatively, it may be only the perceptions that differ, perhaps consequent to depression, a state in which otherwise neutral stimuli may be experienced as negative. Future studies that prospectively establish the nature and number of life events in perimenopausal women with and without depression may allow for the discrimination between the actual

occurrence of adverse events and depression state-related reporting biases.

The second question that we addressed was whether the co-occurrence of hot flushes with perimenopausal depression resulted in a different pattern of life event reports. For example, it has been suggested that symptoms associated with hot flushes (e.g., ongoing disruption of sleep) may cause depression in some perimenopausal women. Further, Joffe et al. (2002) reported that hot flushes and depressed mood were correlated in perimenopausal women but not in pre- or postmenopausal women. Thus in the presence of hot flushes, the putative role of life events in the development of depression would be expected to be diminished. In our data the presence or absence of hot flushes did not influence the number or quality of life events reported in either the depressed or the non-depressed perimenopausal women. Thus the stress or life disruption secondary to hot flushes did not necessarily result in either depression or reports of increased negative life events. Similarly, in a separate study we observed that the therapeutic response to estradiol occurred independent of the presence of hot flushes (Schmidt et al., 2000). Thus, although hot flushes may induce a more pronounced sleep disturbance in perimenopausal depression, the presence of hot flushes does not appear to alter the relationship between life events and the onset of depression.

We compared the reports of life events in depressed women with and without a past history of depression to examine a potential reporting confound. We observed no differences in the reported number of exit or negative life events. As a further protection against the influence of a past history of depression (present in half our patient sample) on our results, we re-performed our comparisons of patients and controls in a subgroup with *no* history of depression. Results were unchanged. Thus, negative life events have a significant association with the onset of perimenopausal depression in this sample of women, regardless of the presence of a past history of depression.

Previous studies have suggested that negative life events are more relevant to the onset of less severe depressions (Paykel et al., 1996; Maciejewski et al., 2001). However, Ormel et al. (2001) observed that the role of stressful life events did not differ between major and subsyndromal depression, consistent with a variety of clinical characteristics (noted below) that fail to distinguish major from minor depressions. Thus, the Ormel et al. data would suggest the relevance of our findings to both perimenopausal major and minor depressions. Minor depressions, by definition, have fewer and less

severe symptoms than major depressions (Rapaport et al., 2002). Nonetheless, they are associated with disability comparable to that of major depression (Broadhead et al., 1990; Judd et al., 1996). In fact, major depressions of moderate severity are not distinguished from minor depressions by family history, course (i.e., both major and minor depressions occur in subjects over their lifetime), or biological characteristics (Rapaport et al., 2002; Akiskal et al., 1997).

The depressed perimenopausal women also reported significantly less satisfaction with their significant others, suggesting that group differences in the perceived level of marital support and, possibly, social support could exist. Certainly, the perception of marital quality may reflect a depressed state-dependent perception of the marriage (Birtchnell, 1991) and not the true quality of the relationship. However, if present, reduced marital support could contribute to the reports of an increased number of both negative events and events that negatively impacted on self esteem in the depressed perimenopausal women compared to controls. Longitudinal studies tracking the onset of depression, the number and quality of life events, and measures of social and marital support should assist in clarifying the nature of the relationship between negative life events at midlife and perimenopause-related depression.

Although, our data suggest the lack of relevance of the "empty nest" syndrome in the experience of depression during the perimenopause, they also emphasize the importance of the relationship between negative life events, marital support and self esteem in perimenopausal depression independent of the presence of hot flushes. Moreover, despite studies documenting the therapeutic efficacy of estradiol (Schmidt et al., 2000; Soares et al., 2001) (as well as the presumed efficacy of more traditional antidepressant therapies), efforts to reduce life stress and to improve social support and feelings of self efficacy may be beneficial in women with perimenopause-related depression. Finally, as a caveat, given the retrospective nature of the instrument that we employed, the modest sample size, and the cross-sectional study design, our findings must be confirmed in larger, longitudinal designs.

References

- Akiskal HS, Judd LL, Gillin C, Lemmi H (1997) Subthreshold depressions: clinical and polysomnographic validation of dysthymic, residual and masked forms. *J Affect Disord* 45: 53–63.
- Ballinger SE (1985) Psychosocial stress and symptoms of menopause: a comparative study of menopause clinic patients and non-patients. *Maturitas* 7: 315–327.
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. *Arch Gen Psychiatry* 4: 561–571.
- Birtchnell J (1991) Negative modes of relating, marital quality and depression. *Br J Psychiatry* 158: 648–657.
- Broadhead WE, Blazer DG, George LK, Tse CK (1990) Depression, disability days, and days lost from work in a prospective epidemiologic survey. *JAMA* 264: 2524–2528.
- Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 301: 291–293.
- Chou KL, Chi I (2000) Stressful events and depressive symptoms among old women and men: a longitudinal study. *Int J Aging Hum Dev* 51: 275–293.
- Cooke DJ, Greene JG (1981) Types of life events in relation to symptoms at the climacterium. *J Psychosom Res* 25: 5–11.
- Dennerstein L, Leher P, Dudley E, Guthrie J (2001) Factors contributing to positive mood during the menopausal transition. *J Nerv Ment Dis* 189: 84–89.
- Dennerstein L, Dudley E, Guthrie J (2002) Empty nest or revolving door? A prospective study of women's quality of life in midlife during the phase of children leaving and re-entering the home. *Psychol Med* 32: 545–550.
- Dohrenwend BS, Krasnoff L, Askenasy AR, Dohrenwend BP (1978) Exemplification of a method for scaling life events. The PERI Life Events Scale. *J Health Soc Behav* 19: 205–229.
- Ezquiaga E, Gutierrez JLA, Loepz AG (1987) Psychosocial factors and episode number in depression. *J Affect Disord* 12: 135–138.
- Greene JG (1983) Bereavement and social support at the climacteric. *Maturitas* 5: 115–124.
- Greene JG, Cooke DJ (1980) Life stress and symptoms at the climacterium. *Br J Psychiatry* 136: 486–491.
- Halbreich U, Endicott J, Schacht S, Nee J (1982) The diversity of premenstrual changes as reflected in the Premenstrual Assessment Form. *Acta Psychiatr Scand* 65: 47–65.
- Holmes TH, Rahe RH (1967) The social readjustment rating scale. *J Psychosom Res* 11: 213–218.
- Joffe H, Hall JE, Soares CN, Hennen J, Reilly CJ, Carlson K, Cohen LS (2002) Vasomotor symptoms are associated with depression in perimenopausal women seeking primary care. *Menopause* 9: 392–398.
- Judd LL, Paulus MP, Wells KB, Rapaport MH (1996) Socioeconomic burden of subsyndromal depressive symptoms and major depression in a sample of the general population. *Am J Psychiatry* 153: 1411–1417.
- Kendler KS, Thornton LM, Gardner CO (2000) Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. *Am J Psychiatry* 157: 1243–1251.
- Locke HJ, Wallace KM (1959) Short marital-adjustment and prediction tests: their reliability and validity. *Marr Fam Liv* 21: 251–255.
- Maciejewski PK, Prigerson HG, Mazure CM (2000) Self-efficacy as a mediator between stressful life events and depressive symptoms: differences based on history of prior depression. *Br J Psychiatry* 176: 373–378.
- Maciejewski PK, Prigerson HG, Mazure CM (2001) Sex differences in event-related risk for major depression. *Psychol Med* 31: 593–604.
- Murrell SA, Meeks S, Walker J (1991) Protective functions of health and self-esteem against depression in older adults facing illness or bereavement. *Psychol Aging* 6: 352–360.
- Ormel J, Oldehinkel AJ, Brilman EI (2001) The interplay and etiological continuity of neuroticism, difficulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. *Am J Psychiatry* 158: 885–891.
- Paykel ES (2001) The evolution of life events research in psychiatry. *J Affect Disord* 62: 141–149.

- Paykel ES, Prusoff BA, Uhlenhuth EH (1971) Scaling of life events. *Arch Gen Psychiatry* 25: 340–347.
- Paykel ES, Cooper Z, Ramana R, Hayhurst H (1996) Life events, social support and marital relationships in the outcome of severe depression. *Psychol Med* 26: 121–133.
- Radloff LS (1977) The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1: 385–401.
- Rapaport MH, Judd LL, Schettler PJ, Yonkers KA, Thase ME, Kupfer DJ, Frank E, Plewes JM, Tollefson GD, Rush AJ (2002) A descriptive analysis of minor depression. *Am J Psychiatry* 159: 637–643.
- Schmidt PJ, Nieman L, Danaceau MA, Tobin MB, Roca CA, Murphy JH, Rubinow DR (2000) Estrogen replacement in perimenopause-related depression: a preliminary report. *Am J Obstet Gynecol* 183: 414–420.
- Soares CD, Almeida OP, Joffe H, Cohen LS (2001) Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry* 58: 529–534.
- Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W, Woods N (2001) Stages of Reproductive Aging Workshop (STRAW). *J Women's Health Gend Based Med* 10: 843–848.
- Spitzer RL, Endicott J (1979) Schedule for affective disorders and schizophrenia – lifetime version. Biometrics Research Department, New York State Psychiatric Institute New York, NY.
- Spitzer RL, Williams JB, Gibbon M, First MB (1990) Structured clinical interview for DSM-III-R, patient edition. Biometrics Research Department, New York State Psychiatric Institute New York, NY.
- Tennant C, Andrews G (1976) A scale to measure the stress of life events. *Aust NZ J Psychiatry* 10: 27–32.
- Veeninga AT, Kraaijaat FW (1989) Life stress and symptoms in menopause clinic patients and non-patients. *J Psychosom Obstet Gyn* 10: 269–277.

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