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Review

Depressive disorders and the menopause transition

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ABSTRACT

Aim: Depressive disorders and symptoms are common among middle-aged women. The effects of hormones on depression remain unclear. This review aims to clarify the nature of depressive disorders during the menopause transition as well as their links with climacteric syndrome, sexuality, cardiovascular risk and cognitive function.
Material and methods: The recent literature on depressive disorders and menopause is reviewed.
Results and conclusions: Women are more vulnerable than men to depressive disorders. Endocrine influences have been postulated but differences in, for example, coping style and response to stress may also contribute to the gender difference in the prevalence of depressive disorders. Gender differences in socialization may lead to higher rates of depression in women. There are data top suggest that menopause and depression are associated, although there is not a common clear causative factor. Women with climacteric symptoms (hot flushes, night sweats, vaginal dryness and dyspareunia) are more likely to report anxiety and/or depressive symptoms. Bothersome vasomotor symptoms could be associated with sleep disturbances, which in turn can increase reports of anxiety and depressive symptoms. Biopsychosocial and partner factors have a significant influence on middle-aged women's sexuality and depressive disorders, and most antidepressants can have a negative effect on sexual response. Lastly, studies have consistently shown that women with high levels of depressive symptoms are at greater cardiovascular risk and have poorer cognitive function than non-depressed women. At present, a direct relationship between psychiatric symptoms and hormonal changes such as estrogen decrease has not been clearly found. Stress, educational level, ethnicity, socioeconomic factors and partner status may influence the prevalence and clinical course of both menopause symptoms and depressive disorders. Since in many cases depression is a lifelong condition, and is associated with severe comorbid conditions, further studies are needed to improve the early diagnosis of depression; it may be advisable to monitor a woman's mental health during the menopause transition to prevent a depressive disorder having long-term negative consequences.

Contents

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CIRS, Cumulative Illness Rating Scale; CSFQ, Changes in Sexual Functioning Questionnaire; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; DISF, Derogatis Inventory of Sexual Function; HT, hormone therapy; OR, odds ratio; POAS, Penn Ovarian Aging Study; PRIME-MD, Primary Care Evaluation of Mental Disorders; SCID, Structured Clinical Interview for DSM Disorders; SSRIs, selective serotonin reuptake inhibitors; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; SWAN, Study of Women's Health Across the Nation.

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1. Introduction

Depression is the most common of all the psychiatric disorders, and its incidence is increasing (or at least had previously been under-reported) [1]. Globally, at the beginning of the 21st century, the prevalence of depression is 5.8% for men and 9.5% for women, with variations according to the studied population and the diagnostic criteria or rating instruments used [2–7]. In Europe, the lifetime prevalence of major depression is estimated at 12.8%, but with a substantial gender difference, at 9.2% for men and 18.2% for women [8]. Compared with men, women have an earlier age at onset of depression, more frequent depressive episodes, more depressive symptoms and much higher rates of atypical depressive features [9]. It can similarly be said that men report fewer symptoms than women and that men reach the diagnostic threshold less often [10,11]. Thus, women are more vulnerable to depressive disorders than men. Differences in coping styles and response to stress may contribute to this gender difference [12–15].

Because depressive disorders seem to be almost twice as common in women as in men, endocrine influences on the prevalence and clinical characteristics of depression have been postulated. Further, many women experience mood disorders in association with the low-estrogen phase of the menstrual cycle, after childbirth and during menopause. Since depressive symptoms are especially common among middle-aged women, the purpose of this update is to review recent information concerning depression and the menopause transition.

2. Depressive disorders, hormones and menopause

The potential relationship between depressive disorders, hormones and menopausal stages has been the object of intense controversy. The hypothesis that irregular patterns of hormone production during the perimenopausal transition increase vulnerability to mood disorders in susceptible women is supported by increased prevalence rates as well as animal and human studies [15–17], although there are no definitive answers to this question [18,19].

2.1. Surgical menopause

Women who undergo surgically induced menopause have higher rates of depression than those who undergo natural menopause [20]. Apart from abrupt hormonal changes, psychological reactions to the loss of the reproductive organs could play an important role, depending of the patient's disposition. Age, sex, social status, profession, family support, the reasons for the operation and the importance of the organ to the patient's identity can all influence the reaction to organ loss. Psychiatric problems such as depression, agitation, insomnia, non-specific anxiety, phobias, psychosomatic disorders and psychosexual problems have been reported after hysterectomy and/or oophorectomy [21]. Moreover, a sample of women admitted to a psychiatric hospital for depression had a higher incidence of hysterectomy and/or oophorectomy [22].

On the other hand, several longitudinal studies have reported that most patients perceive an overall improvement in quality of life, depressive symptoms included, after hysterectomy and oophorectomy, which supports the concept that menopausal complaints depend on a multitude of factors other than hormone levels alone [23,24]. Indeed, some studies suggest that psychiatric symptoms decrease after surgery as quality of life and sexual functioning improve [24]. Aziz and colleagues [25] reported that, with or without oophorectomy, hysterectomy improves general health and psychological well-being, reduces depression and improves sexual satisfaction, interest and frequency. Flory et al. [26] reviewed 100 articles published in the last 30 years, and reported that hysterectomy did not generally cause psychosocial problems; however, in 10–20% of the women, sexual interest, arousal and orgasm decreased, whereas depressive symptoms and impaired body image increased.

The effects of abrupt estrogen deprivation after oophorectomy appear to be different in premenopausal and postmenopausal women. In younger women (under 48 years of age), surgical menopause was associated with an increased lifetime risk for the development of mood and anxiety disorders [27] and these young women may be at greater risk for depression than older women following hysterectomy [28]. In addition, in the Mayo Clinic Cohort Study of Oophorectomy and Aging, women who had both ovaries removed before reaching natural menopause experienced a long-term increased risk of depressive and anxiety symptoms, parkinsonism, and cognitive impairment or dementia [29].

In a secondary analysis of data collected in a cohort study of 1047 premenopausal women undergoing hysterectomy with or without concomitant oophorectomy for benign indications, the effect of bilateral oophorectomy on postoperative depressive symptoms varied: there was a decrease in the risk of depressive symptoms in women without baseline depressive symptoms, but the risk did not change in those with baseline depressive symptoms [30].

Hormonal changes induced by premenopausal bilateral oophorectomy are different from those occurring during natural menopause or those induced by postmenopausal bilateral oophorectomy. Bilateral oophorectomy before menopause results not only in an abrupt drop in levels of circulating estrogen but

also an abrupt drop in levels of circulating progesterone and testosterone. By contrast, if the ovaries are removed long after a woman has experienced natural menopause, the hormonal changes related to estrogen, progesterone, and gonadotropins may be less dramatic, because estrogen and progesterone levels are already naturally reduced. However, the postoperative drop in testosterone levels is also abrupt in these postmenopausal women and may have clinical consequences. In this respect, several mechanisms linking bilateral oophorectomy with age-related neurological diseases have been suggested, especially in those women already genetically more prone to experience age-related neurological disease [29].

2.2. Estrogens

Two different hypotheses link estrogens with the development of depression during and after the menopause transition: (1) low levels of estrogens are associated with depressed mood; and (2) the unstable and irregular pattern of hormone production during the menopausal transition increases vulnerability to mood disorders in susceptible women. Epidemiological studies have found inconsistent results concerning the first hypothesis (Table 1). While some studies have not found such an association [31–33], others have found a higher prevalence of depressive symptoms during the perimenopause than in the postmenopause [34].

The second hypothesis has also mixed support: two studies confirm it [35,36] while two studies reject it [33,37] (Table 1). The study of Freeman et al. [35] found that both the onset of depressive symptoms assessed with the Center for Epidemiologic Studies Depression Scale (CES-D) and the presence of major depressive disorder diagnosed using the Primary Care Evaluation of Mental Disorders (PRIME-MD) are associated with increased variability of estradiol levels (around the woman's own mean). In agreement with this, the Melbourne Women's Midlife Health Project [36] showed an association of depressive symptoms with a 2-year decline in estradiol levels but not with absolute hormone levels. However, neither the longitudinal Study of Women's Health Across the Nation (SWAN) [37] nor the Penn Ovarian Aging Study (POAS) [33] found such associations. Bromberger et al. [37] did not find any significant association between either the level of estradiol or change in that level and the severity of depressive symptoms (CES-D score $\geq$16 or $\geq$22), while Morrison et al. [33] failed to find any association between depressive symptoms (CES-D scores again) or major depression (PRIME-MD) with estradiol levels through the menopause transition.

A more recent paper examined the association between common estrogen receptor alpha gene variants and the lifetime incidence of major depression and the risk of recurrent depressive episodes in older women. The GG genotype of rs9340799 was found to be associated with higher risk of recurrent depressive episodes [38,39]. Preliminary data suggest that estrogen receptor alpha polymorphisms are indeed associated with mood and cognitive outcomes [40].

2.3. Androgens

Findings from studies that have investigated a possible association between depressive symptoms and dehydroepiandrosterone (DHEA) or dehydroepiandrosterone sulfate (DHEA-S) are variable. While some studies have found a negative association [31,41], others have reported a positive association [33,42], and still others have failed to find any association [38]. The two longitudinal studies produced contradictory results (see Table 1). In the 11-year follow-up POAS report, Morrison et al. [33] found a positive association between plasma DHEAS-S levels and scores on the CES-D through the menopause transition; nonetheless, they failed to find an association between the incidence of major depression and plasma DHEA-S levels, although its odds decreased during the menopausal transition. The baseline POAS [43] also reported an association between plasma DHEA-S levels and depressive symptoms (CES-D score), but here the association varied with age: in younger women depressive symptoms were associated with higher DHEA-S levels, while in older women they were associated with lower DHEA-S levels. Furthermore, race influenced the age of this transition between these DHEA-S CES-D relationships: in African American women it occurred at an earlier age than in Caucasian women.

Morrison et al. [33] offer two explanations for the mechanism of the association between DHEA-S levels and depressive symptoms, since neither testosterone nor estradiol played a role: (1) the estrone level, which was not measured, could be responsible for the association; and (2) DHEA-S, a possible positive allosteric modulator of the N-methyl D-aspartate glutamate receptor in the hippocampus, could potentiate the effect of glutamate and thus exert an effect on mood. On the other hand, the SWAN [12] did not find a significant effect of plasma DHEA-S level on the risk of depressive symptoms (CES-D score $\geq$ 16) [37].

The majority of studies have not found any significant association between testosterone plasma levels and depression [31,33]. However, Bromberger et al. [37] recently reported a significant association between both absolute testosterone levels and increased testosterone levels from baseline and a higher risk of depression (defined as a CES-D score either $\geq$16 or $\geq$22). In contrast, Santoro et al. [42] reported a significant negative association between depressive symptoms, also assessed by means of the CES-D, and plasma levels of total and free testosterone.

3. Depressive disorders during and after menopause transition

The association between depressive disorders and menopausal status is an important public health problem that requires attention. Although in 2005 the US National Institute of Health [44] concluded that data on the association between the two were poor or mixed, several studies [34,35,45,46] have since provided good evidence for such an association, and have suggested that the period of greatest vulnerability to new-onset depression in middle-aged women is the transition to menopause, not the postmenopausal period, as previously believed. However, a recent report from Bromberger et al. [47] has created controversy again. The difficulty in finding a consistent, coherent epidemiological trend may be due to methodological limitations, among which the definition and assessment of 'depression' are the most important. It is unfortunate that the majority of studies have focused on depressive symptoms instead of depressive disorders (major depression, dysthymia, etc.). Furthermore, in the few studies where depressive disorders have been investigated, their diagnosis has mainly relied on scores on psychometric instruments or structured interviews.

3.1. Major depression and dysthymia

The reported prevalence rates of current major depression in women vary between 0% [34] and 11% [47] (Table 2). In the premenopause period the reported prevalence rates range from 5.8% to 11% [43,47]; in the perimenopause from <4% to 9.1% [34,47]; and in the postmenopause stage from <1% to 9.8% [34,47]. The prevalence rate for dysthymia was reported to be 4.5% in one study [43]. In premenopausal women followed up for 10 years over the menopausal transition, the odds of having a major depressive disorder (diagnosed by means of the Structured Clinical Interview for DSM Disorders [SCID]) in that period was significantly greater

Table 1
Studies on association between depressive symptoms or clinical depression and hormone levels.

First author, year	Sample size	Type of study	Menopausal status	Association between ...	Association with ...
Schmidt et al. [31]	42	Cross-sectional	Perimenopause	First onset depression (major or minor)	– Decreased levels of DHEA NO significant association with levels of FSH, LH, estrone, testosterone or free testosterone
Seattle Midlife Women's Health Study (SMWHS)					
Woods et al. [32]	302	Longitudinal 10-year follow-up report	Middle and late perimenopause	Depressive symptoms – CES-D	NO significant association with urinary measures of estrone, FSH, testosterone
Melbourne Women's Midlife Health Project (MWMHP)					
Ryan et al. [36]	138	Longitudinal 2-year follow-up report	Postmenopausal (100%)	Depressive symptoms – CES-D shortened version	– 2-year decline in estradiol levels – 2-year increase in FSH levels NO association with absolute hormone levels
Study of Women's Health Across the Nation (SWAN)					
Santoro et al. [42]	2961	Longitudinal Baseline report	Premenopausal (54.1%) early peromenopausal (45.9%)	Depressive symptoms – CES-D score	– Decreased levels of total and free testosterone, and of the free androgen index
Bromberger et al. [37]	3302	8-year follow-up report	Premenopausal Early perimenopausal Late perimenopausal (11%) Postmenopausal (66%)	Depressive symptoms – CES-D ≥ 16 or ≥22	– Increased current testosterone levels – Increase in testosterone levels from baseline NO significant effect of the level of or change of estradiol or FSH No significant association of the DHEA-S level
PENN Ovarian Aging Study (POAS)					
Morrison et al. [43]	338	Longitudinal baseline report	Premenopausal (100%)	Depressive symptoms – CES-D score	– Increased DHEA-S level in the younger half of the sample – Decreased DHEA-S level in the older half of the sample
Freeman et al. [34]	312	4-year follow-up report	Premenopausal (73%) Early transition (21%) Late transition (3%) Postmenopausal (3%)	Depressive symptoms – CES-D	– Rapidly decreasing FSH levels – Aggregate profiles of increasing estradiol levels
Freeman et al. [35]	231	8-year follow-up report	Premenopausal (57%) Early perimenopausal (43%)	Depressive symptoms – CES-D ≥ 16	– Increased levels of FSH – Decreased levels of LH and Inhibin B – Increased variability of estradiol, FSH and LH around the woman's own mean level of each hormone
				Depressive disorders – PRIME-MD	– Increased levels of FSH – Decreased levels of Inhibin B – Increased variability of estradiol and FSH
Morrison et al. [33]	300	11-year follow-up report	Premenopausal (2%) Late premenopause (3%) Early transition (35.3%) Late transition (20.7%) Postmenopause (33.3%)	Depressive symptoms – CES-D	– Increased DHEA-S levels NO significant association with estradiol or testosterone levels
				Major depression – PRIME-MD	NO significant association with DHEA-S, estradiol or testosterone levels

CES-D, Center for Epidemiologic Studies Depression Scale; PRIME-MD, Primary Care Evaluation of Mental Disorders.

during the peri- and postmenopause (odds ratio [OR] = 2.20 and 3.57, respectively) than in the premenopause period [47]. This association was independent of history of major depression, use of psychotropics, adverse life events, reproductive hormone characteristics, body mass index and vasomotor symptoms. However, data from the POAS [35] demonstrated the opposite: the prevalence of depressive disorders identified by the PRIME-MD decreased through the transition (from 11% in the premenopausal period to <1% in the postmenopausal period) [34], and the OR for the onset of depressive disorder during the transition period compared with the postmenopause was not statistically significant [35]. Significant predictors of a major depressive disorder were a history of depression (OR = 4.75), severe premenstrual syndrome, poor sleep, hot flashes [34] and body mass index [35].

Table 2
Prevalence rates of depressive symptoms or clinical depression during and after menopausal transition.

First author, year	Sample (size and characteristics) Type of study	Depression assessment	Prevalence data
The Harvard Study of Moods and Cycles			
Cohen et al. [45]	460 (134 premenopausal and 326 perimenopausal) longitudinal: 7-year follow-up report	Depressive symptoms – CES-D ≥ 16	OR perimenopause compared to premenopause: 1.8
Melbourne Women's Midlife Health Project (MWMHP)			
Ryan et al. [36]	138 postmenopausal Longitudinal: 2-year follow-up report	Depressive symptoms – CES-D shortened version ≥ 10	Prevalence rate: 25.4%
Study of Women's Health Across the Nation (SWAN)			
Bromberger et al. [46]	2885 (25% postmenopausal) Longitudinal: 5-year follow-up report	Depressive symptoms – CES-D ≥ 16	At baseline: 23.1%
			Menopausal stages OR of having CES-D ≥16 compared when they were premenopausal: – Early perimenopause: 1.30 – Late perimenopause: 1.71 – Postmenopause: 1.57 – Hormone therapy users: 1.43
Bromberger et al. [37]	3296 (late perimenopausal: 11%; postmenopausal: 66%) Longitudinal: 8-year follow-up report	Depressive symptoms – CES-D ≥ 16	At baseline prevalence rate: 24.4%
			Menopausal stages OR of having CES-D ≥16 compared when they were premenopausal: – Early perimenopause: 1.31 – Late perimenopause: N/A – Postmenopause: 1.79 – Hormone therapy users: N/A
Bromberger et al. [47] (Pittsburgh site)	221 Longitudinal: 10-year follow-up report	Major depression episode – SCID	Prevalence rates: – Premenopause: 5.8% – Perimenopause: 9.1% – Postmenopause: 9.8% Menopausal stages OR of having a major depression episode compared when they were premenopausal: – Perimenopause: 2.20 – Postmenopause: 3.57
PENN Ovarian Aging Study (POAS)			
Morrison et al. [43]	338 premenopausal Longitudinal: baseline report	Depressive symptoms – CES-D	Mean scores: Caucasian: 13; African American: 17.3
		Depressive disorders – PRIME-MD	All depressive disorders: Caucasian 8.9%, African American 21% Major depression: 8.1% (Caucasian 3.5%, African American 13%) Dysthymia: 4.5% (Caucasian 3%, African American 6.2%) Minor depression: 2.4% (Caucasian 2.4%, African American 2.5%)
Freeman et al. [34]	312 (premenopausal 73%, early transition 21%, late transition 3%, postmenopausal 3%) longitudinal: 4-year follow-up report	Depressive symptoms – CES-D	Mean scores: – Premenopausal: 12.7 – Early transition: 14.6 – Late transition: 13.1 - Postmenopausal: 10.6
		Depressive disorders – PRIME-MD	Prevalence rates: – Premenopausal: 11% – Early transition: 4% – Late transition: 0% – Postmenopausal: <1%
Freeman et al. [35]	231 (premenopausal and early perimenopausal) Longitudinal: 8-year follow-up report	Depressive symptoms – CES-D ≥16	Prevalence rate: 50% Of the 116 women with depressive symptoms: – OR of onset of the symptoms during transition compared to premenopause: 5.44
		Depressive disorders – PRIME-MD	Prevalence rate: 26%

Table 2 (*Continued*)

First author, year	Sample (size and characteristics) Type of study	Depression assessment	Prevalence data
			Of the 59 women with depressive disorders: – OR of onset of the depressive disorder during transition compared to premenopause: 1.6 (p 0.34)
Morrison et al. [33]	300 (premenopausal 2%, late premenopausal 3%, early transition 35.3%, late transition 20.7%, postmenopausal 33.3%) Longitudinal: 11-year follow-up report	Depressive symptoms – CES-D	Mean score: 11.6
		Major depression – PRIME-MD	Current major depression prevalence rate: 5.4%

CES-D, Center for Epidemiologic Studies Depression Scale; OR, odds ratio; PRIME-MD, Primary Care Evaluation of Mental Disorders; SCID, Structured Clinical Interview for DSM Disorders.

3.2. Minor depression/depressive symptoms

Only Morrison et al. [33] have reported data on the prevalence rates of minor depression in middle-aged women. They found that 2.4% of the 338 premenopausal women included in the POAS met the criteria for minor depression using the PRIME-MD. In fact, 'minor depression' is a diagnosis still under study according to the DSM-IV-TR, not a formal diagnosis. Minor depression is defined by the presence of 2–4 depressive symptoms (versus 5–9 required for the diagnosis of major depression) during a 2-week period, and one of these symptoms has to be either depressed mood or loss of interest or pleasure.

With respect to depressive symptoms, again there are contradictory findings (see Table 2). Some studies have reported a higher likelihood of depressive symptoms as women progress through the menopausal transition [37,46], while others have reported a decreased likelihood in the postmenopause [34]. Data from the SWAN have consistently shown significantly increasing OR of having CES-D scores ≥ 16 as women progressed through the menopausal transition (OR in early perimenopause = 1.3, and in postmenopause = 1.79, relative to premenopause) [37,46]. Similar findings were obtained in the POAS [34,35], although the mean CES-D score decreased in the postmenopausal period (from 14.6 in the early transition to 10.6 in the postmenopausal period) [34]. Two studies [45,48] demonstrated a greater likelihood of having CES-D scores ≥ 16 in the perimenopause compared with the premenopause (OR = 1.8 and 5.44, respectively).

3.3. Impact of menopause stages on clinical depression

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study is the first to focus on the influence of the menopause and hormone therapy (HT) on the presentation of major depression. The STAR*D is supported by the US National Institute of Mental Health. It has a total of 4041 participants [49]. The relevant sub-analysis here [50] included 1890 women with major depressive disorder: 50.1% premenopausal, 20.3% perimenopausal, and 29.6% postmenopausal. The premenopausal and perimenopausal women more frequently had a family history of depression than did the postmenopausal women (58% and 63% versus 51%, $p < 0.001$), as well as a personal history of suicide attempts (23% and 20% versus 12%, $p < 0.0001$). The postmenopausal women were older at the onset of their first episode (35.1 years versus 19.0 and 26.6 years, $p < 0.0001$), more frequently presented a chronic depressive episode (37% versus 21% and 26%, $p < 0.0001$), had a greater duration of their depressive illness (19.6 years versus 10.5 and 18.4 years, $p < 0.0001$), and greater medical comorbidity, as rated by the Cumulative Illness Rating Scale (CIRS) (scores of 3.9 versus 2.2 and 3.1, $p < 0.0001$).

Differences in symptomatology were as follows: postmenopausal women were more likely to have suicidal ideation than were pre- and perimenopausal women, while premenopausal women were more likely to have irritability than were peri- and postmenopausal women; premenopausal women were less likely to have early awakening than were perimenopausal women, and were more likely to have decreased appetite than were postmenopausal women. In addition, postmenopausal women reported lower physical functioning (SF-12 scores) than did the other two groups (43.4 versus 52.0 and 49.9, $p < 0.0001$). Thus, it seems that depression in postmenopausal women is more related to general medical comorbidity, hormonal factors and/or aging, while in pre- and perimenopausal women it is more akin to a lifelong disorder.

When the authors analyzed the influence of hormone therapy (HT) on the presentation of major depressive disorder, they found that postmenopausal women taking HT were more likely to have recurrent depressive disorder (83% versus 69%, $p < 0.001$) and to endorse lack of involvement in activities (OR = 2.02), and less likely to have melancholic features (OR = 0.53). They also had greater medical comorbidity as assessed by the CIRS (4.5 versus 3.9, $p < 0.005$), and better physical functioning (SF-12 scores) (45.7 versus 43.4, $p < 0.05$). The fact that there were no differences in the severity of depression supports the suggestion that HT is not a treatment for major depression in postmenopausal women [51].

4. Climacteric/vasomotor symptoms and the domino effect

Climacteric symptoms (hot flashes, night sweats, vaginal dryness and dyspareunia) have been associated with depressive symptoms [5,18,52]. In one study, women with moderate to severe depressive symptoms were almost twice as likely to report recent vasomotor symptoms (hot flashes and/or night sweats) than were women with no or only mild depressive symptoms [53]. It may be that depressive symptoms increase the incidence of menopausal symptoms, or at least the reporting of them; conversely, it may be that severe vasomotor symptoms worsen depressive symptoms [54,55], and indeed it appears that postmenopausal women and especially perimenopausal women suffering more bothersome vasomotor symptoms are more likely to report anxiety and/or depressive symptoms than are women who do not experience vasomotor symptoms to the same degree [56].

A link between hot flashes and disturbed sleep, mainly during the first half of night, has been found in several studies of postmenopausal women [48,57]. Although it is difficult to determine whether poor sleep precedes negative mood or vice versa, the

Table 3
Normal sexual function in women: main differences between the old and the new model.

Traditional linear model (Master and Johnson, Kaplan)	New circular model (Basson)
– Relatively discrete non-overlapping phases	– Overlapping phases in a variable sequence
– Genitally focused	– Combines the responses of mind and body
– Discrete dysfunctions (DSM-IV-TR)	– Comorbidity between dysfunctions (DSM-V)

association of mood problems with sleep disruption seems intuitively likely and has indeed been reported in several studies [58,59], although the nature of the association is not fully understood. Campbell and Whitehead [60] suggested that estrogen therapy might decrease psychological symptoms and insomnia by relieving vasomotor symptoms and referred to this possibility as a domino effect. Nowadays, the 'domino hypothesis' includes the notion that sleep disturbances mediate a relationship between vasomotor symptoms and mood problems. In other words, vasomotor symptoms disturb sleep, and sleep disruption causes negative mood [61]. However, links between vasomotor symptoms and mood have not been found in all studies [62]. In a longitudinal study of women with no history of depression, it was found that those who reported a first experience of depressed mood during the menopausal transition were twice as likely to report hot flashes and onset of depressed mood on the same rather than on different measurement occasions, suggesting that hot flashes may contribute to the onset of depressed mood [35]. Sleep problems would be expected to predict worse mood on the following day rather than the same measurement occasion, which therefore suggests that this indirect effect of vasomotor symptoms on mood may occur largely through a mechanism other than sleep disruption. So, the authors reported that although the domino hypothesis may be true in some cases, this is not the whole story, as controlling for sleep problems did not eliminate the predictive value of vasomotor symptoms on mood, which is consistent with an effect of symptoms independent of sleep [61].

Antidepressants have been tried as an alternative to HT for peri- and postmenopausal vasomotor symptoms and mild sleep disorders [63]. Some antidepressants may have a positive global effect on these complaints, and their use has even been proposed in non-depressed women to treat menopausal symptoms [64]. In non-depressed women the decreases in the frequency and severity of hot flashes have been modest, although patients perceived these improvements as meaningful [63,64]. In another study sertraline did not reduce the frequency or severity of hot flashes, but did produce bothersome side-effects [65]. Currently, there is not sufficient evidence to support the use of antidepressants in menopausal women without depression [66].

5. Sexual functioning and the menopause transition

5.1. Female sexual response

Basson [67] re-conceptualized the female sexual response, moving from the traditional linear model to a circular one (Table 3). One of the biggest changes in this model concerns the sexual desire phase. In the new model, sexual desire is a broad concept that includes not only spontaneous desire but also multiple reasons and incentives for instigating or agreeing to sex, motivation, willingness to become receptive, sexual stimuli with appropriate context, and psychological and biological processing [68]. All these components are related to a variety of factors, among them menstrual cycle, age and a new relationship being of prime importance to spontaneous desire. With respect to the arousal phase, the new model highlights the lack of a strong correlation (unlike in men) between subjective arousal and genital lubrication and/swelling response; instead, thoughts and emotions triggered by sexual excitement were the strongest modulators of sexual arousal in women [68].

This new conception of normal sexual function in women implies that a new formulation is required of women's sexual dysfunctions. The provisional draft of DSM-V has incorporated a new sexual dysfunction category, 'Sexual Interest/Arousal Disorder in Women', which follows the new model and includes the previous 'Hypoactive Sexual Desire' and 'Female Sexual Arousal' disorders [69]. The word *desire* was removed from the new diagnoses and *interest* has been substituted, as 'desire' connotes a deficiency and often implies a biological urge.

5.2. Sexual dysfunction and the menopause transition

Bearing in mind the changes recently proposed in this area, it seems obvious that current incidence and prevalence rates have to be taken with caution, as they may be both over- and underestimations. The longitudinal SWAN has aimed to disentangle the roles of menopause and chronological aging in the sexual functioning of women [70]. The SWAN results showed that menopausal transition is associated with changes in levels of desire and vaginal/pelvic pain. At late perimenopause and postmenopause, the reporting of frequent desire was lower than at premenopause (OR 0.62 and 0.50, respectively), while reports of vaginal/pelvic pain was commoner in the early perimenopause and postmenopause (OR 1.37 and 2.04). The menopause transition had no significant effect on the frequency of sexual activity, arousal, importance attached to it, emotional satisfaction, or physical pleasure. With respect to menopause symptoms, night sweats and hot flashes were inversely related to frequency of masturbation, and vaginal dryness was directly related to pain during intercourse and masturbation, and inversely related to arousal, physical pleasure, and emotional satisfaction. Llaneza et al. [71] reported an inverse correlation between scores on the Menopause Rating Scale and scores on the Changes in Sexual Functioning Questionnaire (CSFQ): the greater the psychological and urogenital menopausal symptoms, the worse was the sexual functioning in all CSFQ domains. In middle-aged women, Mezones-Holguín et al. [52] reported that female sexual function, as measured with the Female Sexual Function Index, was inversely associated with depression, yet confounded with urogenital status. In addition, sexual function was inversely associated with both the partner's sexual functioning and the woman's psychological score for menopause-related quality of life, and was positively associated with premenopausal status.

Studies have reported mixed results in relation to sexual desire. While some have found that women during menopause transition and postmenopause have less interest in sex and less sexual desire than premenopausal women, others have failed to find any difference [72]. Longitudinal studies have, though, demonstrated that sexual desire decreases as women reach the postmenopause stage. Avis et al. [70] reported that pain during sexual intercourse increases and sexual desire decreases over the menopausal transition, and Dennerstein et al. [73] reported a decrease in libido (sexual thoughts or fantasies in last month) when progressing from late menopausal transition to postmenopause, but not from early to late menopause.

Several studies have investigated the role that some endocrine markers of the menopause transition play in sexual desire. The estradiol data are quite consistent: studies have not found any relationship, or found only a marginal association. Testosterone data are more complex, in that no associations and positive associations have been reported [72]. Apart from endocrine markers, many biopsychosocial factors could play a role in sexual desire during

the menopause transition. These can be grouped in four categories: (1) factors specific to the menopause transition, such as endocrine markers and symptoms (hot flashes, irritability, depressed mood, vaginal dryness, among others); (2) psychosocial factors, especially social roles and responsibilities (marital status, parenting, employment, among others), emotional closeness with the partner, well-being, self-image, history of sexual abuse, perceived life stress; (3) health-related behaviors such as use/abuse of substances (tobacco, alcohol, and illicit substances), unhealthy diet, sedentary life-style, and (4) somatic illnesses and/or mental disorders, use of medication, etc. [5,12,13,52,55,71,73–76].

With respect to the influence of depressive disorders on sexual functioning in women, data are mixed. Some authors have reported a direct influence of depressive symptoms/disorders in sexual dysfunction [70,77], even in drug-naïve patients, while others have reported the contrary [78]. Llaneza et al. [71] found that the postmenopausal women included in their study had similar CSFQ scores to younger patients with schizophrenia or bipolar disorders [79].

Fabre and Smith [78] demonstrated that the presence of depressive disorders did not increase the prevalence of DSM-IV sexual dysfunction disorders (hypoactive sexual desire disorder 17.7%, sexual aversion disorder 3.4%, female arousal disorder 5.8%, and female orgasmic disorder 7.7%), but it did negatively affect the women's perception of their sexual functioning (Derogatis Inventory of Sexual Function [DISF] scores). Thus, there was a significant negative correlation between scores on the Hamilton Depression Rating Scale and scores on the DISF; that is, the more depressed the women were, the lower was their sexual functioning. Furthermore, DISF domains were differently impaired, with orgasm the most impaired, and sexual desire and sexual arousal the least.

Most antidepressants have sexual dysfunction as an adverse side-effect, and this can lead to high rates of non-compliance with medication. The commoner side-effects include diminished or absent libido, arousal difficulties, poor vaginal lubrication, delayed orgasm and anorgasmia [75,76,80].

6. Depression and cardiovascular risk in middle-aged women

Longitudinal studies have consistently shown that persons with high levels of depressive symptoms, or with a history of major depressive disorder, are more likely to have clinical coronary events than persons without depression [81]. In addition, the changing hormonal milieu during the menopausal transition could contribute to the worsening of the cardiovascular profile [82]. However, depression appears to predict cardiovascular disease independent of menopausal status [37]. A variety of mechanisms could allow depressive symptoms to contribute to an increased prevalence of cardiovascular disease. A recent study reported that depressive symptoms were independently associated with progression of coronary artery calcification in a cohort of middle-aged women [82]. Depression may also contribute to an increased risk of cardiovascular disease via an increase in the visceral fat mass [83], and through an increased risk of metabolic syndrome with a diagnosis of depression [84].

The effects of antidepressant use on cardiovascular morbidity and mortality are unclear. Tricyclic antidepressants can have cardiotoxic effects. In contrast, selective serotonin reuptake inhibitors (SSRIs) cause a secondary depletion of platelet, so might have protective effects against ischemic cardiovascular events [85]. In this regard, observational studies of the medical risks of antidepressants have had mixed results. A prospective cohort study of community-dwelling postmenopausal women in the Women's Health Initiative found that, in these women, antidepressants were not associated with risk of coronary heart disease, and there were no significant differences between SSRI and tricyclic antidepressant use in risk of coronary heart disease, stroke, or mortality, but the authors also suggested that tricyclic antidepressants and SSRIs may be associated with increased risk of mortality, and SSRIs with increased risk of hemorrhagic and fatal stroke, although absolute risks were low [86].

7. Cognitive impairment and the menopause transition

It is well known that estrogens play a critical role in the neurobiology of cognitive functions [87]. Moreover, depressive disorders/symptoms and the associated brain changes have been related to mild cognitive impairment and probable dementia in postmenopausal women over 65 years of age [88]. In this section we try to summarize recent findings in this area.

There is a paucity of studies on the association between cognitive tasks and the menopause transition, although verbal episodic and working memory, processing speed, and verbal fluency have been investigated. Verbal memory is a task of particular interest, since performance in this area can reflect the risk of dementia in later life. Verbal memory declines with normal aging, and peri- and postmenopausal women frequently complain about it [89]. A cross-sectional study did not find significant differences in performance on tasks involving verbal memory among women in the early perimenopause, late perimenopause and postmenopausal stages [90]. Two longitudinal studies on the topic have had mixed results: while the Chicago site of the SWAN study [91] demonstrated a small improvement over time in verbal and working memory not related to menopausal stage, the SWAN study demonstrated an improvement in scores on verbal and working memory only for premenopausal and postmenopausal women [92]. Similar results were found for processing speed, which improved over time during the premenopause, early perimenopause and postmenopause [58]. In the case of verbal fluency, women who transitioned to perimenopause showed significantly less improvement than those who remained premenopausal [93].

Several studies have examined the impact of HT on cognitive functioning, especially verbal memory and the function of medial temporal lobe structures. The hypothesis is that certain forms of HT are beneficial when initiated close to the menopause transition, in the so-called 'critical window' [94]. However, the results are mixed. Studies with conjugated equine estrogens plus medroxyprogesterone acetate showed a worsening in verbal memory, in both younger and older women [95,96]; red clover had no effect [55], and higher doses of estradiol improved it in younger postmenopausal women [87,89].

8. Overpathologizing the menopause?

In some cultures, menopause has positive connotations (for example a sense of relief at moving past the reproductive years), while in others it is linked to negative attitudes such as worries about getting ill and getting old, and feeling less feminine [12,13,97]. Women with more negative attitudes towards the menopause in general report more symptoms during the menopause transition [98].

While the majority of women do not develop depression during the menopausal transition, psychological distress and depressive symptoms have been observed more frequently in some groups of perimenopausal women [99]. On the other hand, studies vary considerably in design, measures of depression, and in consideration of and adjustment for important confounders. This makes it problematic to reach definitive conclusions regarding a possible adverse independent influence of the menopause transition on mood symptoms [100].

In a multivariate model Freeman et al. [34] found women in menopause transition were nearly three times more likely to report depressive symptoms than were premenopausal women. Bromberger et al. [37] also reported an increased chance of a woman having more depressive symptoms during the menopause transition and in the postmenopausal period than during the premenopausal period, after controlling for a range of covariates. Taken together, these studies suggest that a significant number of middle-aged women will report depressive symptoms at some point during the menopause transition, but that stage of the menopause is only one of a range of factors associated with depressive symptoms. Depressive symptoms, though, have generally been measured by self-report mood scales [101]. In contrast, a study that used a standard psychiatric interview did not find any association between first-onset depressive illness and menopausal status; the factors most likely to predict first-onset depressive illness were low role functioning due to physical health, stressful life events, and a history of an anxiety disorder [102].

Diagnosing a depressive disorder requires the identification of characteristic symptoms and depressive cognitions together with associated disability or change in day-to-day functioning. The assessment of depression in middle-aged women during the menopause is difficult, as several of the symptoms included in the diagnostic criteria are common at that time. For example, sleep disturbance and fatigue may simply be the result of the menopause transition and not indicative of depression [57]. For this reason, the diagnostic tools used in some studies, especially the self-report mood scales, could inflate the rate of pathology in women at the menopause transition, especially if they were used on only one occasion, when a single high score could merely reflect transient distress.

According to some authors, the rates of depressive symptoms in middle-aged women are not exceptional and are similar to those at other times in a woman's reproductive life [101]. There is the suggestion that we are may be overpathologizing many women in this respect.

9. Final remarks

Women's responses to menopause vary greatly both within a culture and among different cultures; account has to be taken of traditions, education, and socioeconomic factors. A greater prevalence of depressive symptoms in peri- and postmenopausal women has been reported. In spite of several studies reporting a tendency for depression in women with rapidly changing levels of reproductive hormones, a direct relationship between psychiatric symptoms and hormonal changes (e.g. estrogen decrease) has not been clearly established. Stress, educational level, ethnicity, socioeconomic factors and partner status may influence both menopausal symptoms and the prevalence and clinical course of depressive disorders. Since in many cases depression remains a lifelong disease and is associated with severe comorbid conditions, further studies are needed to improve the early diagnosis of depression during the menopause transition, to prevent it having unnecessary long-term negative consequences.

Contributors

Faustino R. Pérez-López and Plácido Llaneza were involved in conception and design; David Llaneza-Suárez and Begoña Arnott helped in analysis and interpretation of publications; and María Paz García-Portilla did the drafting of the manuscript. All authors were involved in critically revising the manuscript for its intellectual content; and the final approval of the manuscript was done by all authors.

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