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Evaluation and management of depressive and anxiety symptoms in midlife

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ABSTRACT

Objectives Evaluation and management of anxiety and depression during the menopausal transition are complicated by the overlap between some symptoms of affective disorder with those of menopausal symptoms, and also by inconsistencies in the literature regarding the relationship between the menopausal transition and affective disorders.

Methods We have reviewed key studies over the past three decades addressing depression and anxiety during the menopause transition, in order to present a practical, clinical approach to the evaluation and management of anxiety and depressive symptoms at midlife.

Results Symptoms of anxiety and depression are common at midlife and may coincide with menopausal symptoms. Some menopausal symptoms are also symptoms of anxiety and/or depression. Management should include treatment of troublesome menopausal symptoms, providing strategies to deal with psychosocial stressors, and exclusion of clinically significant anxiety and depressive disorders. Interventions such as exercise and cognitive behavior therapy may improve mood and general health at menopause, and a multifocal approach is recommended. Depression of greater than moderate severity requires treatment with an antidepressant. Some selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors may also improve vasomotor symptoms and these should be considered in women with both affective disorder and vasomotor symptoms.

Conclusions There is no clear evidence that the menopause transition alone increases the risk of clinically significant affective disorders, except in women with risk factors such as psychosocial stressors, severe and prolonged vasomotor symptoms and a previous history of affective disorders. Nevertheless, anxiety and depression are common in women and clinicians should be alert to the symptoms of these conditions at all encounters.

INTRODUCTION

Depression and anxiety are highly prevalent affective disorders, associated with significant morbidity and mortality, and are around 1.5–3 times more common in women than men[1]. Women have significantly more first occurrences of depressive disorder, but there are no sex differences in chronicity or recurrence[1]. Generalized anxiety disorder (GAD) is the most common of the anxiety disorders, with an estimated population prevalence of 3%, and is the second most common condition presenting to the general practitioner[2]. The key feature of GAD is uncontrollable worry across a number of domains, and unpleasant symptoms of physiological arousal.

Midlife (from 45 to 55 years) generally spans the menopause transition. Midlife commonly coincides with other major changes including physical health problems, changes in family and professional roles, changes in relationships and sexual functioning, or new care-giving roles in relation to aged parents or ill partners[3,4]. The menopausal transition (MT) commences with the onset of first menstrual irregularity, or infrequent menses, and ends with the final menstrual period (FMP)[5] and has a highly variable duration. Vasomotor symptoms affecting around 80% of women last for around 4 years. For a significant minority, vasomotor symptoms may persist for many years[6]. The median age of onset of menstrual irregularity and of the FMP are about 47 years and 51 years, respectively[7].

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REVIEW

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The MT is marked by wide fluctuations in sex steroid hormones[8] and a variety of vasomotor, psychological and psychosomatic symptoms. There is considerable controversy surrounding which symptoms can reliably be attributed to the menopause and there are marked cultural variations. The NIH State of the Science Consensus[9] concluded that vasomotor symptoms (hot flushes and night sweats), vaginal dryness and sleep disturbance were core menopausal symptoms. Muscle aches and pains are also commonly reported at menopause and are improved by estrogen[10]. Whilst mood changes such as irritability and depression are commonly reported and included as part of rating scales used to quantify severity of menopausal symptoms[11], their status as core menopausal symptoms is uncertain[12]. Menopause involves complex personal, social and cultural connotations. For example, women with more negative attitudes towards the menopause in general report more symptoms during the MT[13].

The apparent increase in depression and anxiety in females during the reproductive lifespan has led to the hypothesis that these disorders in women are endocrine-dependent. The increased incidence of premenstrual and postpartum mood disorders further supports this hypothesis[14]. Recent US guidelines advise that all midlife women should be screened for depression[15].

Evaluation and management of affective disorders at menopause are complicated by the similarity between some symptoms of anxiety and depression, such as fatigue, concentration and subjective memory problems, sleep disturbance, sexual dysfunction, and palpitations and common symptoms of menopause. The challenge for the clinician is to determine which symptoms are attributable to menopause, and may be amenable to menopause therapies, and which are due to mental health disorders and require psychological or psychiatric management. These difficulties are compounded by unresolved controversy in the literature regarding the precise relationship between changes in reproductive hormones and both depression and anxiety in midlife women[16,17].

The purpose of this review is to explore key studies undertaken over the past three decades reporting data on depression and anxiety during the menopause transition, in order to present a practical, clinical approach to the evaluation and management of anxiety and depressive symptoms in these women. This approach takes into consideration the potential overlap between anxiety symptoms and vasomotor symptoms, and the potential value of hormone replacement therapy (HRT) to improve function.

METHOD

Medline and PsychINFO databases were searched by entering the key terms 'depression', 'depressive disorder', 'midlife', and 'menopause'. Articles were also obtained by following up references listed in articles. Twelve studies (28 articles) providing cross-sectional and/or longitudinal data examining the cause and prevalence of depression in mid-age women were identified. Studies of anxiety published between 1980 and 2011, using the Medline, Web of Science and PsychINFO databases using the key terms 'anxiety', 'anxiety symptoms', 'anxiety disorder', 'menopause', 'menopausal transition', 'midlife', 'hot flushes or flashes' and 'vasomotor symptoms' were sourced. Articles were also obtained through publishers' email alerting services and manual searching of references identified in the articles obtained. Included studies were in English, reported original research using a clearly described measure of anxiety, and investigated either the prevalence or severity of anxiety during both natural and induced menopause, or the relationship between anxiety and vasomotor symptoms. The majority of the studies reviewed measured anxiety symptoms, rather than anxiety disorder. Nine studies reporting the relationship between menopause and anxiety symptoms, two studies reporting the prevalence of an anxiety disorder, namely panic disorder, and eight studies investigating the relationship between anxiety symptoms and VMS were identified.

RESULTS

Depressive symptoms in midlife

Women at risk of depressive symptoms in midlife are more likely to have a past history of depression[18], premenstrual mood disturbance[19,20] and postpartum mood disorders[19]. In addition, depressive symptoms are more common in those with severe and prolonged vasomotor symptoms[18], psychosocial stressors[19] and physical health problems[18,19]. Many of these factors are also associated with an increased risk of depression during other stages of life, and so are not specific to depression during the MT.

The majority of women do not develop depression during the MT, and longitudinal studies are conflicting regarding the MT as a risk factor for depressed mood (see reference 16 for review). Direct comparisons between studies are limited by differences in design, measures of depression, and in adjustment for important confounders. Two recent longitudinal studies[21,22] have identified the menopausal transition as an independent risk factor for depressive symptoms in midlife women, with an increased risk of 1.5–3-fold[22]. Risks of depressive symptoms were doubled in those with a history of depression. Other significant predictors of depressive symptoms included severe premenstrual symptoms, poor sleep, and lack of employment. The stage of the MT may also be significant. Bromberger and colleagues[21] reported that other risk factors include financial difficulties, negative attitudes to aging/menopause, and stressful life events. Taken together, these studies demonstrate that a significant number of mid-age women do report depressive symptoms at some time, but that stage of the MT is only one of a range of factors which are associated with depressive symptoms as measured by self-report mood scales in midlife.

Depressive illness in midlife

Depressive illness differs from depressive symptoms in severity and duration of symptoms, and in degree of suffering or

functional impairment. The relationship between menopause and depressive illness is not well defined. Three large population-based studies have measured the incidence of new-onset depression in the MT. All used menstrual bleeding pattern to identify menopausal status; two also measured reproductive hormone levels[21,22]. Definition of new-onset depression varied between studies, as did frequency of assessment and duration of follow-up. Two studies[22,23] found an increase in new-onset depressive disorder during MT. However, both studies were limited by mixed methods to diagnose depression. Further, known risk factors for depression were not consistently recorded including physical illness, substance use, family history of depression and stressful life events. In contrast, the third study[21] used a standard psychiatric interview, the Structured Clinical Interview for DSM-1V Disorders (SCID), conducted by trained interviewers, at annual assessments over 7 years. They also examined a range of health-related factors and stressors. They found no association between first-onset depressive illness and menopausal status. The factors most likely to predict first-onset depressive illness during the MT were low role functioning due to physical health, stressful life events, and a history of an anxiety disorder. Perception of the effect of physical health on role functioning nearly doubled the risk of first onset.

The prevalence of anxiety during the menopausal transition

The prevalence of anxiety during the menopause transition is not known. The published literature is limited in both quantity and quality and contains several cross-sectional and longitudinal studies of anxiety symptoms, but comparisons are limited by differing methodology. 'Anxiety' is a general term that can obscure the important distinction between anxiety symptoms and anxiety disorders. Anxiety encompasses diverse symptoms such as feeling on edge, worrying, specific fears, and physiological arousal, and these may be distressing to the individual in their own right. Anxiety disorders, such as generalized anxiety or panic disorder, however, are defined by reference to specific criteria and have much lower prevalence than anxiety symptoms.

Anxiety symptoms may be increased during the MT, but the prospective relationship between anxiety symptoms and menopause stage is poorly understood[24–26]. Some studies report that levels of anxiety symptoms rise during the menopause transition, and then fall[18,26]. Others report that anxiety is not related to menopausal stage[25,27], but rather to other lifestyle factors, such as being overweight and low participation in exercise.

Similarly, the relationship between menopause and panic attacks or disorder is poorly characterized. Many studies have failed to control for known risk factors for anxiety such as depression, alcohol use and lifestyle factors. One study reporting the prevalence of panic disorder assessed with a diagnostic instrument, namely the SCID (Structured Interview for DSM-IV (www.scid4.org)[28], highlights the overlap of the symptoms of panic disorder with vasomotor symptoms. This case–control study of panic disorder in a small sample ($n = 45$) of women attending a menopause clinic reported that 18% of the participants had panic disorder, of whom 62% reported onset of panic disorder at the commencement of menopause, and 38% reported worsening of symptoms at this time. In a large community-based sample ($n = 3369$ postmenopausal women aged 51–83 years) using a retrospective questionnaire, Smoller and colleagues reported a 10% prevalence of panic attacks in postmenopausal women and found that women with panic attacks had an increased risk of coronary heart disease and stroke[29]. These were postmenopausal women and the prevalence of anxiety may be higher in women during the menopause transition[26]. However, panic attacks alone do not meet the clinical criteria for panic *disorder*.

The relationship between anxiety or depression and vasomotor symptoms

There are clear similarities between symptoms of menopause and those of anxiety. Both may include the rapid onset of unpleasant, physical sensations, such as palpitations, and rapid changes in temperature perception, and both are associated with increased metabolic rate and noradrenergic dysregulation[30]. Anxiety symptoms are common in women with depression. Moreover, symptoms of fatigue, concentration and memory problems, sleep disturbance, weight changes and sexual dysfunction are common to depression and to menopause. These similarities may make the evaluation of anxiety and depressive symptoms in women with vasomotor symptoms complex and problematic. Some measurements of anxiety, such as the Zung Anxiety Index, have a strong somatic focus, making them particularly unsuitable for use in women with vasomotor symptoms. Independent evaluation of cognitive and somatic symptoms of anxiety has suggested that menopausal women may have artificially increased scores for the somatic symptoms of anxiety due to vasomotor symptoms[31].

Objective measures of VMS suggest that higher anxiety levels increase the perception but not incidence of VMS[32]. These findings may indicate key mechanisms underlying hot flushes, as well as pointing towards new interventions to modify the perception of troublesome vasomotor symptoms at menopause[33]. Hunter and Mann[13] have proposed a cognitive model of hot flushes that integrates a number of biological, environmental and psychological variables. They propose that the experience of hot flushes is shaped by individual differences in symptom perception, cognitive appraisals of those symptoms, and beliefs about menopause and makes VMS a target for cognitive therapies.

For the clinician, the important message appears to be that both anxiety and depression are common in midlife women and that management of these disorders during the menopausal transition is likely to be multi-modal, taking into account psychological and social factors as well as endocrine and other physical changes and the nature and severity of menopausal symptoms and their impact on quality of life. The following considerations may be useful in evaluating and

managing women at midlife with symptoms of anxiety and depression.

INVESTIGATING AND MANAGING DEPRESSIVE AND ANXIETY SYMPTOMS AT MENOPAUSE

For women presenting to a gynecologist, endocrinologist or general practitioner with menopausal symptoms, the key recommendation is to consider the possibility that depression or anxiety may accompany these symptoms. These symptoms may be coincidental or may be exacerbated by menopausal symptoms. In addition, underlying anxiety may increase the perception or impact of menopausal symptoms. Non-specific symptoms such as palpitation may arise due to several causes and should not be attributed to menopause without consideration of other underlying physical or psychological causes.

Diagnosis of a depressive disorder requires the identification of characteristic symptoms, such as persistent low mood, loss of interest and pleasure, tearfulness, as well as depressive cognitions, such as thoughts about guilt or worthlessness, or self-harm and suicide, together with impairment in day-to-day functioning. These symptoms should be elicited by careful clinical interview covering the presence of physiological symptoms of anxiety, such as feeling keyed up or nervous, the presence of intrusive worries, and avoidance of situations because of the anxiety they provoke. It is important to remember that depression and anxiety commonly co-exist. If an affective disorder is suspected, input from a mental healthcare professional can assist in confirming the diagnosis and in planning management. Careful evaluation is required to identify biological, psychological or social factors contributing to the onset or maintenance of an affective disorder. The patient may require multidisciplinary care, to address management of menopausal symptoms as well as mental health problems.

The management of depression in women in midlife follows the broad principles applied at other life stages. The approach should be bio-psycho-social, and specific treatments will vary according to the severity of the disorder. Whilst HRT is not an antidepressant[34], it may improve depressive symptoms in women with hot flushes and should be considered in those with mild depressive symptoms and no other contraindications (see Figure 1)[35,36]. For those with moderate severity disorder, psychological therapies focusing on the multiple life changes which may occur in midlife are appropriate. Importantly, organic factors, other than the endocrine changes of the menopause which may lead to depression, should be considered. Common organic causes of depression include thyroid dysfunction, autoimmune disorders and malignancy of various types. Clinicians should also consider the possibility that depression is occurring secondary to another psychiatric disorder such as anxiety, early dementia or a paranoid illness, or is associated with drug or alcohol addiction. Lifestyle interventions such as exercise may improve psychosocial functioning and also health-related quality of life[37]. Depression of greater than moderate severity requires treatment with an antidepressant. Some selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors may also improve VMS and these should be considered in women with both affective disorder and VMS[36]. Severe depression may require treatment with electroconvulsive therapy.

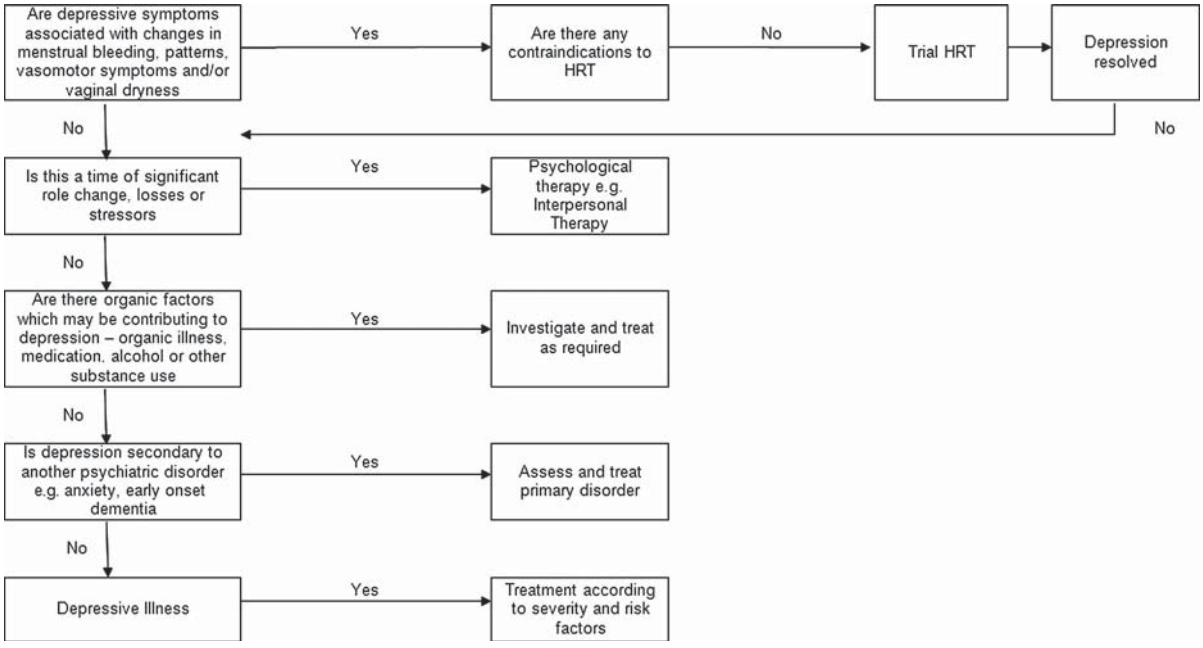

Figure 1 Assessment and management of depression in mid-age women

The approach to anxiety management in menopausal women is similar to that taken with adults at other life stages, but needs to consider the unique features of the menopausal transition. These include the high prevalence of VMS and disturbed sleep, the effects of VMS on daily functioning, the possibility of relationship problems secondary to menopausal symptoms such as vaginal dryness, and the psychosocial context of this life stage. In midlife, women commonly juggle multiple roles and role transitions, which may be sources of stress and anxiety, and these may require therapeutic intervention. For some women, anxiety is focussed on their VMS, and this can be addressed by a clinical psychologist using a cognitive-behavioral model of hot flushes that integrates biological, environmental and psychological variables. A useful behavioral strategy is to learn controlled breathing to manage hot flushes, while challenging catastrophic thoughts may help women to feel more in control of their VMS[38].

Interventions will depend on the type of anxiety disorder (e.g. GAD or panic disorder), severity, and any associated conditions (such as depression) and/or risk factors (see Figure 2). Lifestyle factors, such as weight management and exercise, may be particularly important in women with troublesome VMS and may require support from a physiotherapist or dietician.

CONCLUSIONS

Symptoms of depression and anxiety are common during the menopause transition. These symptoms may be due to an affective disorder, may be associated with psychosocial stressors or may be part of normal changes during the MT. In clinical practice, it may be difficult to distinguish symptoms of anxiety and depression from those of menopause. However, when these symptoms are pervasive and affect daily function despite management of VMS, the possibility of an affective disorder should be considered. Given the high prevalence of anxiety and depression in the general population, clinicians should be alert to the possibility of these disorders and their multi-factorial etiology in every clinical encounter. If an affective disorder is diagnosed, treatment should follow the broad principles applied at other life stages. The approach should be bio-psycho-social, with specific treatments varying according to the severity of the disorder.

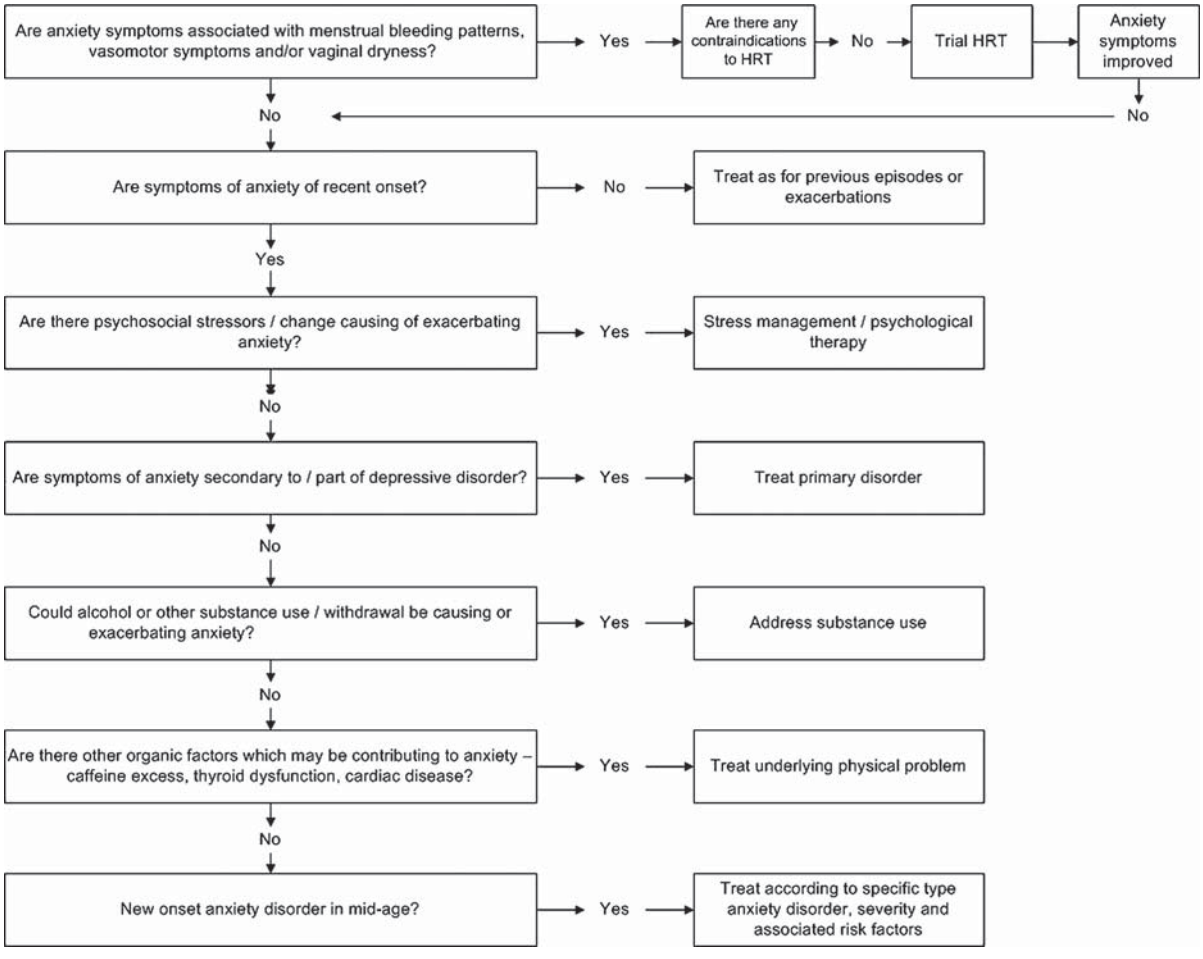

Figure 2 Assessment and management of anxiety in mid-age women

Conflict of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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