Curr Psychiatry Rep (2015) 17: 93
DOI 10.1007/s11920-015-0636-3

Diagnosis and Treatment of Anxiety in the Aging Woman

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Published online: 13 October 2015

Abstract The peri- and postmenopausal periods represent a window of vulnerability for emergence of anxiety symptoms and disorders in the life cycle of adult women. Compared to depression, anxiety symptoms and disorders remain largely unexplored during this phase of a woman's life, despite the significant impact on quality of life if not diagnosed and treated. Here, we review the literature to present our current understanding of the epidemiology, causal factors, diagnosis, and treatment of anxiety in the aging woman.

Keywords Menopause · Perimenopause · Postmenopause · Anxiety and aging · Estradiol · HPA axis · Diagnosis · Treatment · Medication · Psychotherapy

Introduction

The climacteric years represent a significant transition in the life cycle of women worldwide, with underlying changes in biological and psychological functioning converging to increase risk of experiencing a new or recurrent mood disorder. While it has been established that a woman's risk of depression increases dramatically during the perimenopausal transition and then declines in the postmenopausal years [1–4], relatively few studies have systematically examined the relationship between anxiety and menopause. We have conducted a review of the literature to present our current understanding of the epidemiology, causal factors, diagnosis, and treatment of anxiety in the aging woman. We will also first present a case as an example of anxiety in an aging woman.

Case Vignette

Mrs. R is a 56-year-old female who was referred to the Penn Center for Women's Behavioral Wellness by her gynecologist for evaluation and management of increasing anxiety. The patient reported a worsening anxiety and hot flashes for several months although she had a history of mild anxiety throughout adulthood. She reported a 2-year history of menstrual irregularity and her last menstrual period was 9 months prior to the evaluation. She characterized her symptoms as overwhelming anxiety when she woke in the morning, with physical symptoms of shakiness and stomach upset as well as a nonspecific feeling of fear. This lasted for at least 15 min and then subsided partially, with some generalized worry and tension lasting throughout the day. She experienced daily hot flashes, which would sometimes be associated with worsening anxiety. She intermittently felt sad, was less motivated to do things that she usually enjoyed, but denied persistent depressed mood.

She attributed her increase in anxiety, in part, to several life changes and psychosocial stressors. She had recently moved with her husband to the city from the suburbs, and her father was diagnosed with Parkinson's disease and her daughter was recently married. She also described worry about aging, changes in her physical appearance, and greater ease at being injured during routine exercise. She reported a decline in

This article is part of the Topical Collection on *Women's Mental Health*

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short-term memory beginning the previous year. While these memory changes worried her, she denied any impairment in her daily functioning or her role as the director of a nonprofit organization.

With respect to previous treatment strategies, a short trial of venlafaxine ER 75 mg taken daily was associated with significant side effects and no change in anxiety or vasomotor symptoms. She had seen a psychiatrist once in the past for management of her fear of flying for which she was prescribed a benzodiazepine for a short course as needed. She had no psychotherapy trials. Medical history was significant for headaches and irritable bowel syndrome. She had two normal pregnancies, denied postpartum depression or significant premenstrual mood symptoms. She had no medical or family history contraindications to the use of hormone therapy but denied any previous use.

On mental status exam, the patient was mildly anxious and had no evidence of cognitive impairment. Initial assessment was of generalized anxiety disorder, likely exacerbated by changes related to perimenopause and significant life transitions. She agreed to a trial of escitalopram, preferring this option to hormone replacement therapy or psychotherapy.

Epidemiology

Anxiety disorders are highly prevalent worldwide, affecting 15.7 million people in the USA each year, occurring twice as often in women than in men [5]. Although the incidence of these disorders peaks in the fourth decade, the menopause transition and the postmenopause may be periods that pose some risk for development of these symptoms or exacerbation of previously existing symptoms. Although studies have not specifically focused on each of the anxiety disorders, the prevalence of anxiety symptoms during midlife in women appears to be high. Studies report up to 51 % of women aged 40 to 55 experiencing nervousness or irritability within the past 2 weeks [6] and 25 % experiencing these symptoms frequently [1]. In one large retrospective study of 8000 women aged 45 to 54 years, 23 % of subjects reported experiencing anxiety symptoms during the past 6 months [7]. Another longitudinal analysis of data from the multisite Study of Women's Health Across the Nation, involving 2956 woman of varying ethnicities aged 42–52 at study entry, followed for 10 years, women with low anxiety at baseline were more likely (odds ratio 1.56–1.61) to report high anxiety at perimenopause or postmenopause compared to premenopause [8•]. Some conflicting evidence exists, however, with two other prospective studies failing to demonstrate an increase in anxiety during menopause [9, 10]. As indicated in the "Case Vignette," the presence of hot flashes or vasomotor symptoms have also been associated with increased risk of anxiety during peri- and postmenopause [11, 12]. A prior history of a depression or premenstrual mood symptoms may increase risk for anxiety symptoms, as demonstrated in a prospective 9-year analysis of 404 women in the Penn Ovarian Aging Study [13]. Certainly anxiety symptoms can be as debilitating as depressive symptoms, and anxiety has been found to negatively correlate with quality of life indicators in perimenopausal women. A cross-sectional multivariate analysis of menopausal symptoms reported by 150 women found that anxiety, fatigue, and sleep disturbance accounted for 16.7 % of the variance in quality of life [14]. Anxiety during peri- and postmenopause has also been shown to correlate with self-reported interference with work and relationships [15].

Although anxiety disorders may decrease in prevalence in older adults, including women, they are still frequent, with prevalence as high as 15 % in community samples and 28 % in clinical samples [16]. While many of these cases involve chronic anxiety beginning earlier in life, anxiety can develop for the first time in old age, particularly in women. One study found new-onset anxiety disorders in 11 % of older women, compared with 2 % of older men [17]. A review of European epidemiological studies found that the incidence of agoraphobia may increase over the lifespan in women [18]. Additionally, as seen in younger populations, anxiety is highly comorbid with depression. In a study of 182 depressed subjects 60 years and older by Lenze and colleagues, 23 % of subjects had a current anxiety disorder diagnosis and 35 % had at least one lifetime anxiety disorder diagnosis [19]. Risk factors include female sex, chronic medical conditions, cognitive impairment, disability, and previous history of anxiety disorder [20]. Other work has suggested that the presence of anxiety disorders in the elderly contribute to morbidity. One cross-sectional study of community-dwelling elderly living in Mexico City found a correlation between clinical anxiety and frailty (defined as poor resilience and low physiological reserve) [21]. A 1-year longitudinal study showed that anxiety is associated with cognitive decline [22]. There is also evidence that anxiety disorders and symptoms are associated with unfavorable health outcomes and activity limitations [23, 24•].

Some research has focused more specifically on the prevalence of panic attacks in older women, rather than more generalized anxiety symptoms. A cross-sectional survey of 3369 postmenopausal women, aged 50–79, involved in the Women's Health Initiative study demonstrated that 17.9 % of participants had recently experienced a panic attack [25]. The study did not determine if women met full criteria for panic disorder, however, which is much less common than experiencing a panic attack. Other research suggests a low prevalence of panic disorder in women over 65 [26]. Younger women, who were closer to the menopause transition, were more likely to have recently had panic symptoms than the older subjects. Even after adjusting for depression and medical illness, panic attacks were associated with functional

impairment. Therefore, most current evidence suggests that anxiety, in various forms, is prevalent and can have clinically significant impact on women in the peri- and postmenopause.

Biological Causal Factors

Recent studies investigating the role of ovarian and stress hormone fluctuation in perimenopausal depression may indicate a shared biological vulnerability to anxiety. Anxiety and depression are both thought to involve dysregulation of the monoaminergic pathways in the central nervous system, and changing estrogen levels can lead to alterations of these serotonergic and noradrenergic systems. In animal models, estrogen administration can induce changes in serotonin neurotransmission in the amygdala, hippocampus, and hypothalamus, brain regions which are involved in affect regulation. In humans, studies of menopausal women undergoing estrogen treatment showed changes in mood as well as serotonin transmission relative to hormonal status [27, 28••]. One hypothesis proposes that increased variation in ovarian hormone levels during the menopausal transition leads to mood disturbance. Freeman and colleagues, in the Penn Ovarian Aging Study, found a positive correlation between syndromal depression, depressive symptoms, and estradiol variability in perimenopausal women euthymic at baseline [29]. While several other studies found no relationship between these variables [3, 30], the work of Freeman et al. had the advantage of more frequent hormone level sampling, providing increased sensitivity to subtle changes in the hormonal environment during menopause. Furthermore, some evidence suggests that hormonal variation also increases the risk of vasomotor symptoms during the menopausal transition [31], a symptom cluster shown to positively correlate with anxiety during this period [11, 12].

Gordon et al., writing in the *American Journal of Psychiatry* this year, offer an alternative hypothesis whereby impaired gamma-aminobutyric acid (GABA) receptor modulation of the HPA axis may result in a prolonged stress response in susceptible women during the menopausal transition [32••]. It is well established that GABA limits the activity of the HPA axis after stress in addition to having anxiolytic effects [33–35]. The benzodiazepines, which are GABA agonists, are well known as effective anxiolytics. ALLO, a metabolite of progesterone, is a positive allosteric modulator at $GABA_A$ receptors and decreases in concentration during the menopausal transition as there are more anovulatory cycles [36]. Less ALLO, in turn, may thereby reduce GABA-ergic tone and inhibition of the HPA axis, putatively resulting in increased risk of depression and anxiety.

In the postmenopause, other physiologic changes in addition to being hypogonadal could play a role in the continued risk for anxiety disorders. Vascular changes and neurodegeneration, which have been proposed as mechanisms for late-life depression, may also contribute to worsening anxiety. Similarly, women who experience cognitive changes during perimenopause may become unduly worried and anxious about early-onset dementia. Although cognitive complaints are commonly reported by perimenopausal women, it is not likely that these symptoms are associated with neurodegeneration [37•]. In fact, studies suggest a majority of women experience memory problems during this stage of life [38, 39]. Perimenopausal and postmenopausal women have shown deficits in areas of executive functioning (i.e., planning, organization, attention, working memory) [40•, 41]. The causal relationship between anxiety and cognitive decline in the postmenopause requires further investigation. However, we believe a reasonable hypothesis posits cognitive decline as causing anxiety in a subset of postmenopausal women by triggering a fear response directed at impending functional decline.

Psychological Causal Factors

Menopause is a time of significant change in how many women view their roles in society and within the family unit. Women may be retiring or returning to the workforce after having stayed at home to care for their children. They could be experiencing divorce or change in marital roles as their children leave the home. Death or illness of parents and loved ones are common stressors and often cause women to shift into the caregiver role. The loss of fertility occurs within the context of aging and its consequent challenges, including medical illness and reconciling with the often unrealistic public and media romanticization of female beauty and youth [42]. Several studies have demonstrated that women who experience increased psychosocial stressors (i.e., financial hardship, stressful life events, poor social support) around the menopausal transition are more likely to develop major depressive disorder or depressive symptoms [43, 44•]. Additionally, negative views toward menopause have been shown to increase the risk of depressive symptoms during the menopausal transition. In the Study of Women's Health Across the Nation (SWAN), a national multiethnic sample of 12,226 women between the ages of 40 and 55 were assessed on their attitudes toward menopause and aging [45]. Those with a neutral or negative outlook on menopause and aging were almost three times as likely to experience a high level of depressive symptoms (Center for Epidemiologic Studies Depression (CES-D) Scale total score >16) compared to women with a highly positive outlook [43]. It is possible that these attitudes could contribute to anxiety symptoms as well.

Additionally, as there is a potential correlation between anxiety and the presence of hot flashes, women who are prone to anxiety symptoms could be triggered by the presence of feeling overheated and sweating, possibly feeling a similar lack of control that can occur with a panic attack. Women with

co-occurring panic attacks and hot flashes, however, can often distinguish between the two. In a study of 80 postmenopausal women between the ages of 50 and 64, Lermer and colleagues found that somatic anxiety was associated with severity of hot flashes, whereas affective anxiety did not significantly correlate with hot flash severity [46].

Research also has focused more specifically on the psychological and social risk factors for the development of late-onset anxiety disorders in the geriatric population. Similar to late-life depression, cognitive impairment, chronic health conditions, poor self-rated health, functional limitations, personality traits such as neuroticism, and poor coping skills put patients at risk for anxiety disorders [20]. Anxiety disorders are also more commonly seen in those who are childless, have lower income, and have history of trauma. Of course, stress related to the aging process and change in societal roles could also contribute to anxiety in postmenopausal women. Significant losses often continue and contribute to fears of further loss and death. Additionally, social isolation is common and can worsen in the context of anxiety. On the other hand, adaptation and acceptance can occur which may account for the decrease in mood and anxiety disorders in the geriatric population generally compared to younger adults.

Diagnosis and Treatment Considerations

Diagnostic Challenges

Diagnosis of clinically significant anxiety in older women is complicated by the more frequent co-occurrence of depression, age-related psychosocial changes, and the influence of symptom overlap stemming from medical comorbidity [47]. Women may not report their concerns to their provider if they assume that their anxiety symptoms are expected as part of the normal menopause. Alternatively, they may present to their general medical providers or gynecologist with symptoms that they may not identify as anxiety. Anxiety symptoms can include physical symptoms such as with a panic attack, including shortness of breath, racing heart, and sweating. Alternatively, symptoms may be of a variety commonly exhibited in generalized anxiety disorder (i.e., tension, fatigue, headache, and gastrointestinal upset). These symptoms are sometimes difficult to distinguish from the vasomotor symptoms of the menopause transition or the vague symptoms commonly associated with the aging process. Certainly, other medical illnesses should be ruled out, especially in aging women who have higher risk for illnesses, such as cardiovascular disease, pulmonary disease, and cancer. Even when providers recognize that psychiatric treatment is appropriate, women may not agree to a psychiatric referral. Providers may need to initiate treatment despite having limited experience managing psychiatric medications. Treatment may also be indicated for clinically significant anxiety symptoms that interfere with a patient's functioning even if not meeting criteria for a specific anxiety disorder. Programs that involve collaboration between gynecologists and psychiatrists and offer women psychiatric treatment in a setting targeting women with similar concerns are ideal for reducing stigma and barriers to treatment.

Treatment Options

Pharmacologic Management

First-line treatment of anxiety disorders involves psychotherapy, medication, or a combination thereof. Treatment for anxiety is tailored to patient preference and severity of symptoms, and a similar approach is necessary in treating aging women. More severe symptoms may best be treated with a combination of pharmacotherapy and psychotherapy, and milder symptoms may be managed by either option alone.

Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are the first-line medications used in treatment of anxiety disorders, with benzodiazepines often utilized while initiating treatment. Although there are no studies exploring the use of medications for the treatment of anxiety during perimenopause, we do have positive evidence for their use in treating depression in these populations. The SSRI escitalopram proved superior to a combination of estrogen and progesterone in treating depression in a sample of perimenopausal women, with 75 % of women on escitalopram achieving remission of depression compared with 25 % on hormone replacement therapy [48]. Several different SSRI/SNRI antidepressants have been shown to be effective in treating perimenopausal vasomotor symptoms as well [49]. There is additional evidence for the use of SSRIs and SNRIs in the treatment of generalized anxiety disorder in geriatric populations including men and women [50]. When using these medications in older women, it is appropriate to start at the lowest effective dose and to titrate slowly in order to avoid side effects. As older patients may have other medical issues and take other medications, choosing medications with the fewest potential drug-drug interactions is appropriate. In terms of side effects, reduction in libido and sexual dysfunction may be of particular concern in this population as patients may already struggle with these issues due to aging.

Benzodiazepines are also frequently used in the treatment of anxiety disorders, but caution should be taken when utilizing these medications in older women. Short-term use at low doses is recommended, with more concern for side effects such as cognitive difficulties, delirium, and increased fall risk in this population [51]. Additionally, practitioners must be mindful of the risk for benzodiazepine use disorder or misuse

among geriatric patients, which has been shown to increase with age and the presence of comorbid medical conditions for which multiple medications are prescribed [52]. Female geriatric patients tend to receive benzodiazepines for prolonged periods of time [53]. They are more likely than younger patients to use the medications as prescribed but are still at risk for physical dependence and withdrawal [54]. Recent evidence has also shown an association between prolonged use of benzodiazepines and risk for dementia [55].

Hormone therapy (HT) is helpful in treating vasomotor symptoms and may improve sexual function if vaginal atrophy was contributing. Finally, estradiol treatment is more effective than placebo in the treatment of depression with onset during the perimenopause [56]. It may be reasonable to initiate a trial of HT when anxiety occurs in the context of frequent vasomotor symptoms. Using HT in older, postmenopausal women is not typically recommended due to its association with risks for cardiovascular disease and stroke and the reduction in beneficial effects of HT the further a woman is from her final menstrual period [57].

Psychotherapy

There are few studies of psychotherapy for anxiety in older women, but evidence suggests that psychotherapies are helpful in treating geriatric anxiety [58]. Cognitive behavioral therapy (CBT) is highly effective for treating anxiety disorders in younger patients, and several studies in older patients have also demonstrated successful results [50]. CBT should therefore be considered as a first-line option in older populations. Interpersonal and psychodynamic psychotherapies should also be considered in appropriate patients, especially those experiencing distress related to role transitions and conflict associated with aging. There is also growing evidence to support the use of mindfulness meditation programs as adjunctive treatment for anxiety disorders, even in older patients [59]. Multicomponent treatment can therefore be tailored to patient preference and symptom severity.

Future Research

Additional research is needed to investigate the efficacy, safety, and tolerability of SSRIs and HT for treatment of peri- and postmenopausal anxiety. Randomized-controlled trials should be complemented by naturalistic study designs that reflect actual practice (i.e., polypharmacy, multiple medical comorbidities). Further psychotherapy research is also needed. While cognitive behavioral therapy has been shown to be effective in younger patients, its efficacy in the aging woman has yet to be demonstrated.

A richer understanding of the epidemiology of postmenopausal anxiety, with a focus on specific preexisting anxiety disorders, would aid primary prevention as well as allow the clinician to target interventions to women most at risk.

Advances in diagnosis and treatment must occur alongside improvements in the recognition of illness and engagement in care at the point of primary contact. Evidence suggests that perinatal psychiatric illness often goes unrecognized and untreated in the obstetrics clinic [60]. It is reasonable to suspect a similar phenomenon in older women receiving standard care with a gynecologist or primary care physician, who are likely to see the initial presentation of postmenopausal anxiety before it comes to the attention of a psychiatrist. New standards are needed that include diagnostic screening instruments, initial treatment algorithms, protocols governing when to refer to psychiatry, along with continuous evaluation of program performance. The implementation of such standards would create an integrated treatment team that we believe is the ideal model for care delivery in this setting.

Practice Recommendations—Treatment of Mrs. R

After 1 month of treatment with escitalopram 10 mg, and clonazepam 0.5 mg to be used as needed for anxiety, Mrs. R noted a partial improvement in anxiety symptoms and fewer hot flashes. She had no side effects and agreed to increasing escitalopram to 20 mg, and stopping clonazepam, with remission of anxiety symptoms and only occasional hot flashes after 1 month. She remained well for 1 year and then attempted a taper of escitalopram due to concern about sexual side effects. However, her anxiety symptoms recurred. She restarted escitalopram 10 mg/day and experienced resolution of her anxiety with reduced sexual side effects. Had she not responded to escitalopram, a trial of another SSRI would have been reasonable. Additionally, a trial of psychotherapy given her recent life transitions and concern for aging would have been appropriate if she had not fully responded to an antidepressant. HT may have been appropriate for this patient if her vasomotor symptoms had not improved with escitalopram. She is now recommended to remain on an antidepressant as she is at risk for continued anxiety during the postmenopause given her history of having long-standing generalized anxiety.

Conclusion

Although there is a lack of necessary research on the prevalence of anxiety symptoms and disorders in women in the perimenopausal and postmenopausal periods, it is likely that aging women continue to be at risk. Hormonal changes during the menopause transition as well significant life transitions could contribute. Anxiety can certainly lead to poor quality

of life and to worsening of comorbid mood disorders and medical illness. Research shows that depressive disorders in older women respond well to treatment, so treatment of anxiety may have similar response patterns. It will be worthwhile to focus future research efforts on the identification and treatment of anxiety symptoms and disorders in aging women. We can hypothesize that through educational programs targeting primary providers and our older female patients, successful management of anxiety is likely to be achieved.

Compliance with Ethical Standards

Conflict of Interest Andrew M. Siegel and Sarah B. Mathews declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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