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Review article

Strategies to cope with stress and anxiety during the menopausal transition

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ABSTRACT

The menopausal transition is often accompanied by psycho-vegetative symptoms, including stress and anxiety symptoms. Identifying stress and anxiety and intervening early can have an enormous public health impact. Health care practitioners like obstetrician-gynecologists or family doctors play a critical role in the diagnosis, prevention and treatment of stress and anxiety symptoms or disorders, as they often represent women's primary medical contact during the menopausal transition. However, they frequently do not feel confident in identifying and treating mental health problems. The aim of this review was to summarize current (since 2010) knowledge from randomized controlled trials, systematic reviews, and meta-analyses on diagnostics and treatment options, and to provide clinical decision-making algorithms. The recent literature suggests pharmacological, (cognitive) behavioral, and complementary treatments. The choice about which one to use should be discussed with the patient.

1. Introduction

All women will experience menopause (mean age 51) with a gradual decline in ovarian reproductive hormone production starting at age 40 [1]. In most women, peri- and post-menopause are accompanied with several symptoms at varying intensity (climacteric syndrome, International Classification of Diseases (ICD) N95.-). The climacteric syndrome comprises vegetative, physical, psychological, and urogenital symptoms. Overall, up to 80 % of women suffer from the climacteric syndrome, and up to 42 % rate their symptoms as “very severe” with a significant impact on quality of life [2,3].

The hormonal changes accompanying the menopause transition (MT) also make some more women vulnerable to mental health problems. About half of all women report unspecific anxiety, much like lasting premenstrual symptoms, during the MT [4,5]. Additionally, it is overall a time of increased stress, including the experience of stressful life events like a divorce or the loss of a loved one [6]. Due to the close interaction of the reproductive- and the stress axes [7], stress can act as a precipitating or perpetuating factor for disorders like depression or insomnia [8].

Obstetrician-gynecologists (ob-gyns) or family doctors are often the primary medical contact for women during the MT. Studies do, however, show that this group of health care practitioners frequently doesn't feel confident in identifying and treating mental health problems. For example, a study showed that ob-gyns were moderately confident to recognize anxiety, but concerned about whether their training was adequate to make the right treatment decisions [9]. Identifying and guiding women at risk in the clinical practice would have a tremendous public health impact. Therefore, the overarching aim of this article is to summarize existing knowledge on the assessment and treatment of stress and anxiety during the MT. Based on this search and the clinical experiences of the authors, this article moreover aims at providing easy to use treatment algorithms to guide clinical decision-making. The focus will be set on commonly available treatments, including pharmacological (i.

Abbreviations: CBT, cognitive behavioral therapy; CEE, conjugated equine estrogens; COPD, chronic obstructive pulmonary disease; CPA, cyproterone acetate; CRP, C-reactive protein; DSM, Diagnostic and Statistical Manual of Mental Disorders; DYD, dydrogesterone; E2(V), estradiol (valerate); EPT, estrogen-progestogen therapy; ET, estrogen-only therapy; GABA, γ-aminobutyric acid; GAD, generalized anxiety disorder; HRT, hormone replacement therapy; HRV, heart rate variability; ICD, International Classification of Diseases; MCI, mild cognitive impairment; MT, menopausal transition; (M)P, (micronized) progesterone; MPA, medroxyprogesterone acetate; NET(A), norethindrone (acetate); NMG, nomegestrol acetate; PDA, panic disorder with or without agoraphobia; PTSD, post-traumatic stress disorder; RCT, randomized controlled trial; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; SWAN, Study of Women's Health Across the Nations; TCA, tricyclic antidepressant; VMS, vasomotor symptoms.

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e. anti-depressants or hormone replacement therapy, HRT), structured behavioral (i.e. Cognitive Behavioral Therapy, CBT), complementary (i.e. mindfulness), or self-guided ones.

The goal is to provide healthcare practitioners with the knowledge they need to confidently approach stress and anxiety in women who present in their daily practice.

2. Material and methods

For the narrative review on stress and anxiety, we searched the databases Embase, GoogleScholar, and Pubmed. We identified systematic reviews, meta-analyses, or RCTs, published between 2010 and April 2022, using the following MeSH terms: "Stress, psychological", "distress, psychological", "anxiety", "anxiety disorders", "diet", "hormone-replacement therapy", "antidepressive agents", "exercise", "relaxation", "complementary therapies", "Cognitive Behavioral Therapy", "behavior therapy", "physiological stress response", "menopause", "middle aged", "surveys and questionnaires", "systematic review", "meta-analysis", "randomized-controlled trial", plus the individual search terms "psychoeducation", "health education", and "stress-management". The search on stress was completed by SLF and the one on anxiety by PS.

In menopausal women, hormone replacement therapy (HRT) is first-line therapy for the climacteric syndrome, including anxiety symptoms [10–12]. Therefore, a systematic search was performed for the topic of HRT therapy for anxiety. The results of complex literature searches were used that were designed and executed by a medical information specialist for the following information sources to identify all potentially relevant documents on the topics: 1) Medline (Ovid) (incl. Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Medline Daily and Ovid Medline Versions) (1946–February 26, 2022), 2), Embase (Ovid) (1974–February 26, 2022), 3) PsycInfo (Ovid) (1806–February 26, 2022), 4) Cochrane Library (Wiley) (1996–February 26, 2022), 5) Web of Science (Clarivate) (1900–February 26, 2022), and 6) ClinicalTrials.gov (NLM), respectively. Initial search strategies in Medline/Ovid were drafted for four topics (1). Impact of menopause on risk for affective disorders: depression, anxiety, 2) impact of menopause on cognition: in general, MCI risk, dementia risk, 3) impact of HRT on affective disorders: depression, anxiety, 4) impact of HRT on cognition (in general, risk of MCI, dementia) and tested against a list of core references to see if they were included in the search results. Articles were included if women were postmenopausal and taking HRT. HRT was defined as use of systemic estrogens only (ET), systemic estrogen progestogen therapy (EPT), or tibolone at any dosing schedule and dosage. Studies on systemic androgen therapy or only vaginal estrogen therapy were excluded. All original studies, systematic reviews and meta-analyses were included, while editorials, letters, and comments were excluded.

3. Stress

3.1. Definition

Stress results from the imbalance between environmental demands and personal resources to deal with these demands [13]. It is the cognitive appraisal of the event as taxing or exceeding a person's resources that causes a negative affective state. The stress-perception triggers a wide range of physiological responses and behavioral patterns, which are initiated to help the body deal with the threat posed by the stressor [14]. Chronic stress or maladaptive coping strategies can lead to a wear and tear of physiological stress systems. As such, psychological stress is a risk factor for the development, prolongation, acceleration, progression, and relapse of disease, and increases symptom reporting [8]. Stress is closely linked to depression, cardiovascular disease, cancer, metabolic syndrome, later life mild cognitive impairment (MCI), dementia, and Alzheimer's disease, and biological aging [8,15]. In midlife women, stress can increase the risk for sleep problems [16,17], de novo mood disorders [6], and the worsening of pre-existing ones [18]. Moreover, menopausal symptoms such as hot flushes are perceived as more bothersome by stressed women [19,20].

3.2. Prevalence

Women report more stressful life events than men, and the events also seem to have a more negative impact on women [21,22]. Midlife is, particularly for women, a time of increased stress. At the baseline assessment of the Study of Women's Health Across the Nations (SWAN; n = 3284), 42 % of women reported moderate and 19 % high stress in the previous week. Half of all women in the study had moreover experienced one or more stressful life events in the past year [23]. This is comparable to the 40 % of women in the MT, who reported at least one very stressful life event in the past 6 months, including a divorce or separation, a serious illness or death of a close family member, financial worsening or chronic financial problems [6].

3.3. Etiology and risk factors

Stressors can be intrinsic or extrinsic, real or perceived threats to the body's equilibrium. Situations are perceived as particularly stressful, if they are novel, unpredictable, and uncontrollable [24]. Stressors can moreover be distinguished by timescale differences [25] (Table 1). Physiologically, the presentation of an acute stressor triggers the fight-or-flight response, which presents by increases in heart- and breathing rates, muscle tension, as well as the release of stress hormones including the immediate release of adrenaline, norepinephrine, and the delayed release of cortisol. Moreover, systemic inflammatory activity is upregulated. It's through these physiological systems that stress gets under the skin [26]. Negative emotional responses to an acute stressor include anger, sadness, fear, or anxiety. However, the adaptions to the stressor also allow the perception of control by the individual, potentially also rendering stress rewarding, pleasant, or exciting [27]. The behavioral adaption incorporates short-term increases in arousal, alertness, vigilance, attentional focus, and analgesia, to ascertain survival. At the same time, functions which are not important for survival are decreased, including vegetative functions, feeding and reproduction. It's critical that the acute stress response is large enough to overpower the threat posed by the stressor, while also being correlated to the intensity of the threat (neither too large nor too small) and time-limited, to allow the body to return to its homeostatic state once the acute threat is over [26,28].

The biological wear and tear of chronic stress or a maladaptive stress-response can lead to fatigue, vulnerability to infection, and an overall increased risk for disease and mortality [26]. Emotionally, chronic stress goes along with irritability, anger, sadness, a lack of motivation, anxiety, or feeling overwhelmed. Behaviorally, signs of hyperactivation can be found, as well as an increase in substance (ab)use, caffeine intake, social

Table 1
Differentiation between different stressors, based on timescale.

Stressor type/ timescale	Examples
Acute stressors	Immediate events such as a job-interview, giving a speech, or watching disturbing news.
Daily events or daily hassles	More minor events that happen frequently during the day, including deadlines or having to rush to the train or a meeting.
Stressful life events	Time-limited, episodic stressors, like a breakup or receiving the diagnosis of a severe disease. The actual events can be rather short and might also appear as something overall positive (like getting married), but still have long-term consequences and lead to a lasting stress-response.
Chronic stressors	Are experienced for longer periods of time and can include long-term caregiving duties, financial problems, discrimination, or unemployment.

withdrawal, changes in eating behavior (eating more or less), sleep disturbances, or a reduction in the exercising frequency. These maladaptive behaviors can then again increase the risk for disease and all-cause mortality. Moreover, greater perceived stress can amplify menopausal symptoms [29].

3.4. Diagnostics

Patients normally don't present at the clinic because they feel stressed. It's either the symptoms of psychological distress like continuing sleep problems, issues concentrating, pain or pre-existing problems, that suddenly get harder to handle, that have them seek treatment. When trying to rate a patient's stress level, there is need for an integration of perceived and objective stress, life events, and daily hassles. Stressors (triggers or event) can be assessed using validated questionnaires like the *Life Experiences Survey* (LES, [30]), the questionnaire version of the *List of Threatening Experiences* (LTE-Q, [31]), the *Hassles and Uplifts Scale* (HUS, [32]), or the *Social Readjustment Rating Scale* (SRRS, [33]) some of which not only allow the collection of stressors, but also the rating of their valence. Stress perception is also assessed based on psychometric evaluations with the *Perceived Stress Scale* (PSS-10, [34]), *Visual Analogue Scales* (1-item, rated on a 10-point scale), the *Depression Anxiety Stress Scale* (DASS, [35]), or the *Trier Inventory for Chronic Stress* (TICS, [36]). Psychological distress presents when stress is severe and/or prolonged. Distress can present in multiple facets and should therefore be assessed on different levels, including, but not limited to sleep, eating behavior, psychological well-being, affect, somatization, irritability, depression, or anxiety. Examples for validated questionnaires include the *Pittsburgh Sleep Quality Index* (PSQI, [37]), the *Menstrual Distress Questionnaire* (MDQ, [38]), the *Eating Disorder Examination Questionnaire* (EDE-Q, [39]), the *Short-Form 12* or *36* (SF-12 or SF-36, [40]), the *Positive Affect Negative Affect Schedule* (PANAS), the *Beck Depression Inventory* (BDI, [41]), or the *Center for Epidemiologic Disease Depression Questionnaire* (CES-D, [42]). To assess suicidality, the *Columbia Suicide Severity Rating Scale* (CSSR, [43]) can be used, followed up by a personal discussion. Overall distress measures include the Kessler Psychological Distress Scale (K10, [44]). For functional disease, quantifying stress can give an explanation for symptoms and a setpoint for treatment, when a clear physical cause is lacking [45]. To receive a holistic picture of the patient, it is suggested to also assess personal resources like positive well-being and resilience [46,47].

Structured clinical interviews should be used to diagnose any present mental disorders, particularly typically stress-related disorders like depression, anxiety, acute stress disorder, functional somatic disorders, post-traumatic stress disorder (PTSD), or an adjustment disorder. DSM-V codes [48,49] can help distinguish psychosocial and environmental problems that may affect the diagnosis, treatment, and prognosis of mental disorders, but do not fulfill the criteria for any specific disorder (e.g., the burnout syndrome, ICD-10 Z73.0/ICD-11 QD85).

Physiological stress-diagnostics including the assessment of classical stress biomarkers like adrenaline, norepinephrine, cortisol, and C-reactive protein (CRP), are often performed in laboratory research, but rarely used in the clinical settings for stress diagnostics [50,51]. New technological advances allow for continuous stress-assessment in daily life, including heart rate variability (HRV) by affordable consumer devices [52]. Further diagnostics including blood-based tests can be performed for differential diagnoses including thyroid disease, vitamin deficiency, or primary sleep disorders, that overlap with distress symptoms.

Diagnostics should additionally involve the identification of the menopausal stage according to the Stages of Reproductive Aging Workshop (STRAW+10) criteria and menopausal symptoms using validated instruments, such as the *Greene Climacteric Scale* [53], or the *Menopause Rating Scale* (MRS-II) [54].

3.5. Treatment

Considering that stress is a modifiable biopsychosocial risk factor, it is important to routinely ask about stress and intervene as early as possible. In the following, different treatment options are presented, that can be used for stress at varying length and intensity.

3.5.1. CBT psycho- and health education

Most women want to be informed about menopause and any issues that might come along with it [55]. Psychoeducation and health education represent the structured presentation of evidence-based information of health and disease (particularly psychiatric disease in the context of psychoeducation). Education can happen in groups, at the community level, or in one-to-one sessions with patients, and include the presentation of specific information material, workshops, or direct discussions with the health-care provider [56]. The goal is to provide knowledge to foster the understanding of a specific condition and its treatments, and with it, increase compliance, adherence and actively include the patient into the treatment [55]. In the context of stress, women should, for example, receive education about the link between life stress and menopausal symptoms, and the specific interventions they can apply to reduce stress. Studies showed that after receiving a general educational program about menopause, which included topics like stress and stress-management, women had more accurate knowledge, more realistic expectations about menopause, more positive attitudes towards menopause, and less discomfort associated with menopause [55].

3.5.2. Instrumental stress-management

Instrumental stress-management targets the acute stressors and daily hassles [57]. Some stressors are rather typical for the MT or midlife in general. For example, midlife women take up multiple roles in the family, household, work, and leisure time. Often, women hold a sandwich position in the family, having to take care of their own children, but also of elderly parents [58]. This leads to a lack of time for herself and to do things that have value to the woman, outside family or work (e.g., being physically fit or learning new things). Those stressors can be targeted by time-management (e.g., scheduling regular “me time”, leave the house on time) and by delegating task to partners, children, or, if finances allow, outsource things like housekeeping. It's also important to set priorities and think about how women want to spend their time during the work week, evenings, or weekends. This goes hand in hand with acquiring social skills such as “saying no” to less important or less pressing things and recognizing, that the expected negative experiences from declining an offer or invitation mostly don't arrive [57,59].

3.5.3. Mental stress-management

Mental stress-management targets personal stress intensifiers [57], such as beliefs, expectations, or personal motives about how things have to be, should be done, or will become (e.g., perfectionism, rigid health beliefs, catastrophic expectations of menopause). Some women are embarrassed to talk to friends, co-worker, or even the partner about being in the MT, being afraid that this might change the image those people have of her, or that they might not take her as serious as before. There are also women who think it's their fault when they have hot flushes, or who have catastrophic beliefs about what could happen, when she forgets things or does mistakes, due to the lack of sleep at night. Cognitive behavioral therapy (CBT) can help identifying and modifying unhelpful thoughts, beliefs, and expectations [59]. The goal is to identify and challenge automatic beliefs and modify them, to set more realistic expectations and adopt more functional thoughts. Adapting attitudes towards menopause can reduce stress and has been shown to have positive effects on the overall symptom perception [19]. CBT and other psychosocial interventions can increase the quality of life and well-being, with little side effects [55]. Mindfulness exercises can additionally be used to foster the conscious perception of positive experiences [60].

3.5.4. Regenerative stress-management

The last form of stress-management uses evidence-based strategies to target the stress response [57]. There are various strategies to buffer the acute stress response (*palliation*), leading to a quick relief and relaxation, including breathing techniques, diversion, seeking social support by calling a friend, going for a walk, or treating oneself to a nice dinner, or evening at the movies. Long-term regenerative stress-management strategies function to establish regular relaxation and regeneration by preventive and health behavior, in parallel to the cessation of risk behavior (e.g., smoking cessation). Table 2 summarizes available evidence from systematic reviews or RCTs, testing the effect of various strategies on stress-perception, distress, or the physiological stress response.

3.6. Clinical decision-making structure

In Table 3, we present a support matrix, that can aid in the assessment and management of stress in the clinical setting. This matrix is based on the presented evidence and the clinical experience of the two authors.

4. Anxiety symptoms and disorders

4.1. Definition

The most frequent anxiety disorders according to ICD-10 classification are described in Table 4 [61]. However, the term anxiety is often also used to describe symptoms like feeling on edge, worrying, specific fears, and physiological arousal that do not classify for anxiety disorder. Similarly, panic attacks alone do not meet the clinical criteria for panic disorder [62].

4.2. Prevalence

Anxiety disorders are the most prevalent psychiatric disorders and are associated with a high burden of disease [63]. The lifetime prevalence is 14–29 % [61]. Anxiety disorders are most common between 18 and 34 years of age, followed by the 35–49 age group. Women are affected twice as often as men. The 1-year prevalence for any anxiety disorder is 21.3 % in women and 15.4 % for specific phobias. Anxiety disorders often co-occur with other anxiety disorders, depression, somatoform disorders, personality disorders, and substance abuse [64]. However, the prevalence of anxiety (disorders) during the MT is poorly understood [62].

4.3. Etiology and risk factors

The current conceptualization of anxiety disorders assumes an interaction between specific genetic dispositions, manifested in neurobiological changes, and environmental factors (including childhood adversity, stress, or trauma). The focus of neurobiological changes includes neurotransmitters such as serotonin, norepinephrine, dopamine, or GABA, and endocrine alterations affecting, e.g. the hypothalamic-pituitary-adrenal axis. However, to date, none of the putative biomarkers have been shown to be sufficient and specific for the diagnosis of anxiety disorders [61]. The prevalence of anxiety seems to be increased during the MT [65–67], especially when vasomotor symptoms (VMS) are concomitantly present [68,69]. Anxiety has a significant negative impact on quality of life [70] and impairs work life [71]. However, it is unclear whether hormonal changes during the MT have a direct and central influence or whether anxiety occurs as a result of VMS and sleep disturbances and what part other factors may play.

4.4. Diagnostics

Diagnosis of anxiety disorders should be based on ICD-10

Table 2
Regenerative stress-management strategies for peri- and postmenopausal women.

Authors (year)	Article type/ population	Treatment and outcome	Results
Exercise			
Lum & Simpson (2021) [109]	Original publication. Peri- and postmenopausal women.	T: Physical activity during Covid lockdown. O: Perceived stress.	Women who met UK physical activity guidelines had lower stress levels compared to women who showed little or no regular physical activity.
Nigdelis et al. (2018) [110]	Meta-analysis of RCT. Middle aged and older women.	T: Programmed exercise. O: Perceived stress.	Programmed exercise for 6 or 12 months had no effect on perceived stress in middle-aged and older women. The five included RCTs had a high risk of bias, high heterogeneity, and did not include vigorous exercises.
Diet			
Young et al. (2019) [111]	Systematic review of RCT. Healthy or at-risk women and men.	T: B-vitamin supplementation. O: Perceived stress or distress, depressive symptoms, anxiety symptoms.	Benefited stress in healthy and at-risk populations.
McCabe et al. (2017) [112]	Systematic review. Women > 18 years.	T: Essential fatty acid, B vitamins, vitamin C, magnesium and zinc supplementation. O: Perceived stress, cortisol, anxiety.	Essential fatty acids were effective in reducing anxiety, but not stress in menopausal women. Vitamin B6 supplementation lowers anxiety in older women.
Relaxation, mindfulness-based or alternative approaches			
Augoulea et al. (2021) [113]	Original publication (RCT). Peri- and postmenopausal women.	T: 8-week program for stress management or education (control). O: healthy lifestyle, perceived stress, menopausal symptoms.	Helped women adjust a healthy lifestyle (nutrition, exercise, sleep) and implement relaxation, stress management, cognitive restructuring, and self-awareness into the day. Reduction of perceived stress and menopausal symptoms.
Gordon et al. (2021) [114]	Original publication (RCT). Perimenopausal women.	T: Mindfulness-based stress reduction (MBSR) or waitlist control. O: Perceived stress, anxiety, depressive symptoms, resilience, sleep.	Less perceived stress, depressive symptoms, anxiety, increased resilience, and improved sleep in those in the MBSR group. Those with more life stress benefited more from the treatment in their mood.
Zhao et al. (2021) [115]	Systematic review of RCT. Peri- and postmenopausal women.	T: Acupuncture. O: Distress (sleep, depression).	Broad, positive effects on mood and sleep.
Woods et al.	Systematic review. Peri- and	T: Mind-body therapy (MBSR,	MBSR reduced sleep and mood symptoms

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Table 2 (*continued*)

Authors (year)	Article type/ population	Treatment and outcome	Results
(2014) [116]	postmenopausal women.	yoga, exercise). O: Distress (sleep, mood, hot flushes, cognitive symptoms, pain)	and had within-group treatment effects on hot flushes. Yoga reduced hot flushes and improved cognitive symptoms more than exercise, and also had effects on sleep and pain symptoms.
Saensak et al. (2014) [117]	Cochrane review of RCT. Peri- and postmenopausal women.	T: Relaxation. O: Distress (hot flushes, sleep).	Remains inconclusive due to the limited number of publications.
Hormone replacement therapy (HRT)			
Stadler et al. (2019) [118]	Systematic review studies published since 2015. Pre- and postmenopausal women.	T: Combined estrogen and progesterone therapy. O: Cortisol and heart rate variability (HRV).	In two RCT, 3 months treatment did not alter basal cortisol serum levels, while 6 months significantly reduced basal cortisol serum concentrations. No studies on HRV available since 2015.
Herrera et al. (2017) [119]	Original publication. Peri- and postmenopausal women.	T: Estradiol therapy. O: Cortisol response to acute laboratory stress.	Women assigned to estradiol exhibited blunted cortisol responses to the Cold Pressure Task, compared to women on placebo.
von Holzen et al. (2016) [120]	Systematic review. HRT taking menopausal women.	T: Hormone therapy (estrogen only or combined estrogen and progesterone). O: HRV.	Estrogen replacement only: most studies showed an increase in HRV. Combined estrogen and progesterone: Mixed results, with the majority of studies not showing any effect on HRV.
Mindfulness-based apps			
Wu et al. (2021) [121]	Systematic review and meta-analysis. Non-clinical populations of women and men.	T: Smartphone based mindfulness exercises. O: Stress and negative emotions.	Meta-analyses showed positive effects for negative emotions, depressive symptoms, and anxiety symptoms. No effects were found for stress, potentially due to high heterogeneity in stress measures.
Gál et al. (2021) [122]	Systematic review and metal-analysis. Mixed population (some clinical) of women and men.	T: Mindfulness meditation apps. O: Perceived stress, anxiety, depression, psychological well-being.	Meta-analyses showed positive effects for perceived stress, anxiety, depression, and psychological well-being

Note: Whenever no evidence specifically for women in the MT was available, results from broader samples are presented. Abbreviations: HRT = hormone replacement therapy HRV = heart rate variability, MBSR = mindfulness-based stress reduction, O = outcome, RCT = randomized-controlled trial, T = treatment.

Table 3
Clinical decision-making structure to assess and manage stress in the clinical setting.

Question 1: "How is your stress level on a scale from 0–10, where 0 is not stressed at all and 10 is extremely stressed?"
Questionnaires for assessment: VAS.
Examples of patient answers: 0–4 or 5–10.
Strategies: Provide educational materials or general information about stress.
How to proceed: If the VAS rating is between 0 and 4, move on with other examinations. If the VAS rating is between 5 and 10, move on with questions below.

Question 2: "What is it that stresses you out?"
Note: This question targets the stressors. These can be acute stressors, daily hassles, chronically present stressors, or stressful life events.
Questionnaires for assessment: LES, TICS, HUS, LTE-Q.
Examples of patient answers: Work, family duties, symptoms/pain, conflicts, financial issues, own health or health of a relative or close friend, not feeling appreciated or respected, divorce.
Strategies: If acute stressors/daily hassles: Instrumental and mental stress-management. If chronic or stressful life events: regenerative strategies and potentially psychotherapy.
How to proceed: Move on with questions below. For chronic stress or stressful life events, particularly check answers for #7.

Question 3: "Are there any physiological stress symptoms that you noticed, like muscle tension or pain? If yes, how long have these been present?"
Note: It's good to give examples from other patients.
Questionnaires for assessment: SF-36 or SF-12.
Examples of patient answers: I am tense, have more pain in my back, shoulders, or stomach, have migraines or headaches. It's like my heart is pounding out of my chest. This is fairly new. It started weeks ago.
Strategies: If new: palliation strategies. If ongoing: long-term regenerative strategies.
How to proceed: Move on with questions below.

Question 4: "How about your emotional state?"
Note: The basic emotions are sadness, anger, fear, disgust, and joy, however, it is fine if patients use their own words to describe what they feel. Some will name cognitions instead of emotions ("I feel like I can't cope").
Questionnaires for assessment: SF-36 or SF-12, PANAS, K10.
Examples of patient answers: I feel anxious, low energy, drained, on edge, could burst into tears at all times, irritated, frustrated, not ok, sad, angry.
Strategies: Regenerative stress-management: Lower acute stress and adopt long-term stress-management strategies.
How to proceed: Move on with questions below. Particularly check answers for #8.

Question 5: "Did you change your habits? Other people move less when they are stressed, eat more or less than usual, or meet less people? Has anything like this happened for you?"
Note: It's good to give examples from other patients.
Questionnaires for assessment: SF-36 or SF-12.
Examples of patient answers: I exercise a lot less, meet my friends not as often, since I don't have the energy to do so. I lost my appetite/am constantly hungry and crave fatty food. I drink more alcohol or coffee/smoke more. I am less interested in sex.
Strategies: Regenerative stress-management: Lower acute stress and adopt long-term stress-management strategies.
How to proceed: Move on with questions below.

Question 6: "What do you usually do, when you notice those (physiological, emotional, or behavioral) changes?"
Note: This question targets any strategies (adaptive or maladaptive) or health behavior, the patient might show.
Questionnaires for assessment: -.
Examples of patient answers: Not much. I really just wait and hope that it will get better at some point. I drink more coffee to compensate my lack of energy/have a glass of wine or two to relax in the evening.
Strategies: Regenerative stress-management: Lower acute stress and adopt long-term stress-management strategies.
How to proceed: Move on with questions below.

Question 7: "Do you feel like you have strategies you can use to cope with your stress? Are there any things like your family or a hobby, that help you get through this period?"
Note: This question targets potential resources of the patient which can be used or re-activated, in case they are not currently actively accessed.
Questionnaires for assessment: PSS.

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Table 3 (*continued*)

Examples of patient answers: Not many. I could call my friends or kids, but I don't want to bother them/don't have the energy to talk to them. I liked going for walks, but I haven't gone for one in a while.
Strategies: Perform more in-depth psychosocial diagnostics. Potentially needs psychotherapy and/or pharmacotherapy.
How to proceed: Ask for a psychological or psychiatric counsel. Move on with questions below.
Question 8: "Do you experience any other acute symptoms, like sleep issues, depressive symptoms, or hopelessness? Have you ever thought about doing harm to yourself?"
Note: If the lack of sleep is severe, short-term medication might be needed. If there is acute suicidality, accompany the patient to the ER or an emergency psychiatry service.
Questionnaires for assessment: PSQI, ISI, HADS, BDI, CES-D, K10, CSSR.
Examples of patient answers: Yes, I feel hopeless and depressed. I hardly get enough sleep. I thought about how it would be, if I just didn't wake up the next day.
Strategies: Perform more in-depth psychosocial diagnostics. Potentially needs psychotherapy and/or pharmacotherapy.
How to proceed: Ask for a psychological or psychiatric counsel. Move on with questions below.

Abbreviations: VAS = Visual Analogue Scale, LES = Life Experiences Survey, HUS = Hassles and Uplifts Scale, LTE-Q = List of Threatening Experiences, TICS = Trier Inventory for Chronic Stress, SF-36 = Short-Form 36, PANAS = Positive and Negative Affect Schedule, K10 = Kessler Psychological Distress Scale, PSS = Perceived Stress Scale, PSQI = Pittsburgh Sleep Quality Index, ISI = Insomnia Severity Index, HADS = Hamilton Anxiety and Depression Scale, BDI = Beck Depression Inventory, CES-D = Center of Epidemiological Disease Depression Scale, CSSR = Columbia Suicide Severity Rating Scale.

Table 4
Anxiety disorders: short description according to ICD-10 classification, modified according to [61].

Anxiety disorder	Description
Panic disorder with or without agoraphobia (PDA)	Anxiety attacks of sudden onset, with physical manifestations of anxiety (e.g., palpitations, sweating, tremor, dry mouth, dyspnea, feeling of choking, chest pain, abdominal discomfort, feeling of unreality, paresthesia). Panic attacks occur suddenly and increase in intensity during 10 min. They can occur spontaneously, but often they are associated with agoraphobia.
Agoraphobia with or without panic disorder	Fear of places where it might be difficult or embarrassing to escape if a panic attack should occur (e.g., crowds, on public transport, or in closed spaces).
Generalized anxiety disorder (GAD)	In addition to physical symptoms (see panic disorder), psychological symptoms such as impaired concentration, sleep disturbances and nervousness occur. In contrast to the attack-like occurrence of symptoms in panic disorder, the symptoms occur in varying combinations as a subliminal permanent state. In most cases, it is not possible to specify exactly what the anxiety is about. Often worries about one's own worrying occur ("meta-worries").
Social anxiety phobia (SAD)	Fear of situations in which one is the center of attention (e.g., public speaking, visits to authorities).
Specific (isolated) phobias	Phobias restricted to circumscribed situations, often related to animals (e.g., cats or spiders), or other natural phenomena (e.g., blood, heights, deep water).
Mixed anxiety and depressive disorder	The simultaneous presence of anxiety and depression, with neither predominating. However, neither component is sufficiently severe to justify a diagnosis of anxiety or depression in itself.

classification. In primary care, anxiety disorders are often not recognized. This is also due to the fact that many patients do not report anxiety as a leading symptom, but rather somatic complaints (e.g., pain, sleep disorders). Before diagnosing an anxiety disorder, other mental disorders such as other anxiety disorders, major depression, personality disorders, and somatoform disorders must be excluded, as well as physical diseases [61]. Structured or semi-structured interviews such as the *Structured Clinical Interview for DSM-IV* [72] or the *Mini-International Neuropsychiatric Interview* (MINI) [73] can be used to accurately assess symptoms for the diagnosis of an anxiety disorder. These structured interviews are compatible with the DSM or ICD diagnostic systems. Evaluation of anxiety disorder severity at baseline and monitoring of treatment success can be done with diagnosis-specific rating scales. Symptom-specific scales such as the *Hamilton Anxiety Rating Scale* (HAM-A) are no longer used for diagnosis (because then they would compete with ICD or DSM), but only for severity assessment. Examples of symptom-specific scales for panic disorder are the *Panic and Agoraphobia Scale* (PAS), an external and self-assessment tool [74] and the *Panic Disorder Severity Scale* (PDSS), an external assessment tool [75]. Examples of symptom-specific scales for generalized anxiety disorder are the *Hamilton Anxiety Rating Scale* (HAM-A), an external assessment tool [76], and the *Beck Anxiety Inventory* (BAI), a self-assessment tool [41].

In case of menopausal women, anxiety may also be suspected if the menopausal symptom assessment by e.g. the *Menopause Rating Scale* (MRS)-II scores positive on the psychological subdomain (items: depression, irritability, anxiety, fatigue; 5-Likert scale 0 = none to 4 = very severe; categories of psychological impairment: none/minimal: score 0–1, mild: score 2–3, moderate: score 4–6, severe: score $\geq$ 7) [77–79].

Common somatic differential diagnoses of anxiety disorder include pulmonary disorders (e.g., bronchial asthma, COPD, respiratory insufficiency), cardiovascular diseases (e.g., angina, myocardial infarction, arrhythmias), neurological disorders (epilepsy, migraine, multiple sclerosis, other causes of vertigo), otorhinolaryngological disorders (e.g. peripheral vestibular disorder, Meniere's disease, benign paroxysmal positional vertigo), endocrine disorders (e.g., hypoglycemia, hyperthyroidism, menopause, other causes of VMS), and side effects of medications. Therefore, the differential diagnosis of an anxiety disorder includes the following (Table 5):

4.5. Treatment

Treatment is indicated when a patient fulfills criteria for an anxiety disorder as defined by ICD or DSM, shows marked distress, or suffers from the sequelae resulting from the disorder (e.g., suicidality, secondary depression, or substance abuse) [61].

4.5.1. Interdisciplinary guideline-based treatment of anxiety disorders

According to a recent interdisciplinary guideline for the treatment of anxiety disorders [61], treatment comprises psychotherapy, psychotropic drugs, and other interventions (Table 6). First-line medications for

Table 5
Differential diagnosis of anxiety disorder, modified according to [61].

General	Detailed medical history and physical examination incl. vital signs (blood pressure, pulse)
Laboratory assessment	Blood count, fasting glucose, potassium, calcium, thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), thyroid antibodies, Follicle-stimulating hormone (FSH), estradiol (E2), progesterone (P)
Gynecology	Stages of Reproductive Aging Workshop (STRAW) + 10 staging system for reproductive aging in females [1], hormone diagnostics (see above).
Cardiology/internal medicine	(Exercise) electrocardiogram (ECG), possibly 24-hour ECG and/or 24-hour blood pressure measurement, echocardiography, chest X-ray
Neurology	Electroencephalography (EEG), cranial imaging, possibly cerebrospinal fluid diagnostics, Doppler examination
Otorhinolaryngology	Nystagmography, caloric reflex test, vestibularis test, rotation test

Table 6
Treatment recommendations for anxiety disorders in adults [61].

Treatment	Recommendation	Level of evidence	Recommendation grade
Psychotherapy and psychotropic drugs	Patients with PDA, GAD, or SAD should be offered: • Psychotherapy • Medication	Ia	A+
	If psychotherapy or psychotropic drugs are not effective, the other approach or a combination of both should be offered	Expert consensus	CCP+
Psychotherapy and other non-pharmacological options			
Cognitive behavioral therapy (CBT)	Patients with PDA, GAD, SAD, or specific phobias should be offered CBT	Ia	A+
Psychodynamic psychotherapy (PDT)	Patients with PDA, GAD, or SAD should be offered PDT if CBT is unavailable or ineffective, or if they express a preference for PDT after being informed about all available types of treatment	IIa	B+
Virtual reality exposure therapy	Patients with specific phobias can be offered as an adjunctive measure to other standard treatments	Ib	CCP+
	Patients with social phobia can be offered as an adjunctive measure to other standard treatments	Expert consensus	CCP+
Systemic therapy	Patients with SAD can be offered systemic therapy if CBT or PDT is unavailable or ineffective, or if they express a preference for systemic therapy after being informed about all available types of treatment	Expert consensus	0+
Internet-based psychological interventions	Patients with PDA, GAD, or SAD should be offered Internet-based psychotherapeutic interventions (based on CBT for PDA, GAD, or SAD; based on PDT for SAD only) as an adjunctive measure to other standard treatments or to bridge the time until standard psychotherapy begins in the sense of a self-help strategy	Expert consensus	CCP+
Exercise (endurance training, e.g., running 5 km three times a week)	Patients with PDA can be given a recommendation for exercise (endurance training) as an adjunctive measure to other standard treatments	Expert consensus	CCP+
Patient self-help and family support groups	Patients and their families should be informed about self-help and family support groups and encouraged to participate, if appropriate	Expert consensus	CCP+

Abbreviations: PDA = panic disorder/agoraphobia, GAD = generalized anxiety disorder, SAD = social phobia, level of evidence Ia = evidence from a meta-analysis of at least three randomized controlled trials (RCT), level of evidence Ib = evidence from at least one RCT or a meta-analysis of fewer than three RCT, level of evidence IIa = evidence from at least one methodologically sound, non-randomized controlled trial, recommendation grade A+ = "Shall" recommendation: at least one RCT of good overall quality and consistency supports the recommendation directly, without extrapolation (evidence levels Ia and Ib), recommendation grade B+="Should" recommendation: well-conducted clinical trials, other than RCTs, support the recommendation either directly (evidence levels II or III) or by extrapolation (evidence level I) if the studies lack direct connection to the specific topic, recommendation grade 0+ = "May" recommendation: expert committee reports or expert opinion and/or clinical experience of recognized authorities (evidence level IV) or extrapolation from evidence of levels IIa, IIb, or III. This recommendation grade indicates that no directly applicable clinical studies of sufficiently high quality are available for consideration, recommendation grade CCP+ = Expert consensus/clinical consensus point: if no unequivocal evaluation of a relevant clinical topic was possible, recommendations were formulated by expert consensus.

anxiety disorders include selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) (Table 7). When starting pharmacotherapy (SSRI, SNRI), it should be pointed out that the drugs generally take effect only after a latency period of about two weeks. In addition, to improve adherence, information about potential side effects should be provided and medication should be started at half the normally recommended dose. Medication should be administered in the morning or at noon to avoid insomnia, which may occur during the first few weeks of treatment. To reduce the risk of relapse, it is recommended that drug treatment be continued for 6 to 12 months after remission has occurred. To avoid discontinuation syndromes, the dose should be slowly reduced at the end of treatment. For patients who do not respond to medication, additional psychotherapy is usually recommended. If the first medication does not respond after 4–6 weeks of treatment, a second standard medication should be given instead. If there is a partial response after 4–6 weeks, an increase in dose may be considered initially [61].

4.5.2. *Hormone replacement therapy of anxiety symptom relief*

As described in Section 2, a systematic literature search was performed in 2021 which covered the topic "Impact of HRT on affective disorders: depression, anxiety" [80]. Overall, 56 articles were identified that addressed the topic "HRT and anxiety". Of those, 22 were considered suitable for this publication [81–102]. While six publications did not report an impact of HRT on anxiety [81–86], the remaining 16 did [87–102] (Table 8). The latter will be described in more detail. 12 were RCTs [88–92,94,95,97,98,100–102], three prospective cohort studies [87,96,99], and one a cross-sectional study [93], respectively. All but one study [98] included postmenopausal women. Sample sizes ranged from 16 [87] to 419 women [91]. Women were generally described to be healthy. However, the existence and intensity of menopausal symptoms and/or anxiety was not an inclusion criterion in most studies and was not adjusted for in statistical analysis. Only one study specifically included women with significant psychological discomfort at baseline [95]. HRT regimens were very heterogenous in respect to type of

Table 7
Psychopharmacotherapy for anxiety disorders, modified according to [61].

Medication	Drug	Anxiety disorder			Daily dose (mg)	Level of evidence	Recommendation grade
		PDA	GAD	SAD			
SSRI	Citalopram	x			20–40	Ia	A+
	Escitalopram	x	x	x	10–20	Ia	A+
	Paroxetine	x	x	x	20–50	Ia	A+
	Sertraline	x		x	50–150	Ia	A+
SNRI	Duloxetine		x		60–120	Ia	A+
	Venlafaxine	x	x	x	75–225	Ia	A+
Tricyclic antidepressant (TCA)	Clomipramine	x			75–250	Ia	B+
Anticonvulsant	Pregabalin		x		150–600	Ia	B+
Tricyclic anxiolytic	Opipramol		x		50–300	Ib	0+
Azapirone	Buspirone		x		15–60	Ib	0+

Abbreviations: PDA = panic disorder/agoraphobia, GAD = generalized anxiety disorder, SAD = social phobia, level of evidence Ia = evidence from a meta-analysis of at least three randomized controlled trials (RCT), level of evidence Ib = evidence from at least one RCT or a meta-analysis of fewer than three RCT, level of evidence, recommendation grade A+ = "Shall" recommendation: at least one RCT of good overall quality and consistency supports the recommendation directly, without extrapolation (evidence levels Ia and Ib), recommendation grade B+ = "Should" recommendation: well-conducted clinical trials, other than RCTs, support the recommendation either directly (evidence levels II or III) or by extrapolation (evidence level I) if the studies lack direct connection to the specific topic, recommendation grade 0+ = "May" recommendation: expert committee reports or expert opinion and/or clinical experience of recognized authorities (evidence level IV) or extrapolation from evidence of levels IIa, IIb, or III. This recommendation grade indicates that no directly applicable clinical studies of sufficiently high quality are available for consideration.

estrogen (E2(V), CEE, estriol) and progestogen (MP, MPA, NETA, CPA, NMG, DYD, tibolone), EPT combination mode (sequential, continuous), mode of application (oral, transdermal, vaginal, nasal), and dosage (low-dose, standard-dose and high-dose), respectively. Follow-up ranged from two months [98,101] to 10 years [91]. Anxiety assessment methods also varied tremendously. Importantly, none of the studies applied the diagnostic criteria for anxiety disorders described above (Section 3.4). All studies described here reported a beneficial impact of HRT on anxiety symptoms. Some studies showed a beneficial effect of estrogens alone and no additional (positive or negative) effect by the progestogen chosen (DYD [87], CPA [89]). Others observed no impact of estrogens alone but a beneficial impact of EPT on anxiety symptoms (DYD, MPA [95], oral MP at 60 mg/day but not at other dosages [102]). Subgroup analyses found that women with a history of premenstrual syndrome had higher scores of anxiety during the EPT compared to the ET phase [101]. Only one study distinguished between women with and without hot flushes showing that anxiety symptoms were only significantly reduced by HRT in women with hot flushes [88].

4.5.3. Treatment algorithm for menopausal women

Two groups of menopausal women have to be differentiated: 1) Women with a preexisting (treated) anxiety disorder which may exacerbate during the MT, and 2) women who experience anxiety symptoms during the MT for the first time. In the latter group, anxiety symptoms may not fulfill the criteria of an anxiety disorder but may still be irritating and annoying. Importantly, menopausal hot flushes share some characteristics with PDA (e.g., profuse perspiration, palpitations). Also, perimenopausal women with hot flushes are more likely to be depressed [68,103] which again shares characteristics with GAD (e.g., impaired concentration, sleep disturbances). Thus, it is important to disentangle and locate symptoms, and to educate women about the role sex hormones play in symptom occurrence and treatment. Apart from estradiol, the role of progesterone needs special consideration. Progesterone is metabolized to (allo-)pregnanolone which bind to the $GABA_A$ receptor complex in the brain. Depending on dose and concentration these progesterone metabolites have been associated with sedation, anesthesia, anti-epileptic and anxiolytic effects, but also with aggression, irritability and anxiety [102]. This bimodal association must be taken into account when prescribing oral MP to menopausal women. If oral MP increases negative mood, a higher dose might be more appropriate. Usually, in HRT, oral MP at 100–300 mg/day is used for endometrial protection [104], sleep support [105], and VMS relief [106], respectively. However, in an experimental study women received oral MP at single doses up to 1200 mg [107].

Fig. 1 depicts a suggested algorithm on the management of anxiety symptoms in menopausal women, modified according to [62]. First, menopausal symptoms including anxiety symptoms can be assessed by e.g., the MRS-II. If anxiety and other menopausal symptoms and no contraindications towards HRT are present, then HRT can be tried for three months initially. There is some evidence that estrogens enhance mood and improve well-being also in non-depressed perimenopausal women [108]. Furthermore, as transdermal estradiol with MP may prevent the onset of depressive symptoms in euthymic perimenopausal women [108], the preferred HRT regimen would be transdermal estradiol sequentially or continuously combined with oral MP at 100–300 mg/day. Continuous oral MP would have the advantage of providing sleep and calming down support every day. However, if continuous oral MP induces bleeding disorder or has a negative impact on mood (even after increasing the dose), then a sequential regimen with DYD at 10 mg/day would be an alternative.

If anxiety is the only symptom reported, differential diagnostics should be performed as described above. If another cause of anxiety is revealed, the respective primary treatment is indicated. If no other reasons are found, psychotherapy and/or antidepressants can be recommended, or the patient can be directly referred to a mental health specialist, whatever is the preferred strategy after shared-decision making.

5. Discussion

The MT is a critical transition phase and provides an opportunity to address modifiable risk factors like stress and anxiety and integrate health behaviors that support long-term health. This review article summarized evidence covering the assessment, diagnosis, and treatment of stress and anxiety (disorders) during the MT and provides clinical decision-making algorithms which can be applied in the daily practice.

5.1. Practice points

All health care practitioners are encouraged to explicitly ask about stress and anxiety, using the provided open questions, one or several of the cited validated questionnaires, or a structured interview. This article provides easy to use clinical treatment algorithms which can be printed out, to be accessible whenever needed. Several beneficial treatment strategies are presented in this review. The decision about which one to use for a specific patient should always be a collective decision made by the health care practitioner and the patient together. A referral to a different specialty might be needed and should always be considered as

Table 8
Overview of studies investigating the impact of HRT on anxiety symptoms.

Author (year)	Study design	Study cohort (n)	Study cohort characteristics	Intervention	Duration of follow-up	Tool to assess anxiety	Results
Savolainen-Peltonen (2014) [1]	PC-RCT	150 healthy postmenopausal women (n = 72 with hot flushes, n = 78 without hot flushes)	Mean age 53.2 yrs, normal mean BMI	- tE2 gel 1 mg/d - oE2V 2 mg/d - oE2V 2 mg/d + MPA 5 mg/d - Placebo	6 months	Women's Health questionnaire (WHQ)	At BL: significant correlation between hot flushes and anxiety; after 6 months: in women with hot flushes: HRT significantly reduced anxiety; in women without hot flushes: HRT no impact on anxiety
Karsidag (2012) [2]	PC-RCT	130 healthy postmenopausal women	Median age 48.4 yrs	- Tibolone 2.5 mg/d - Placebo	3 months	Beck Anxiety Inventory (BAI)	Anxiety significantly improved in both groups with the tibolone group being significantly superior to the placebo group
Demetrio (2011) [3]	PC-RCT	76 healthy non-depressed hysterectomized postmenopausal women with mild to moderate hot flushes at BL	Mean age 50–51 yrs	- oCEE 0.625 mg/d - Placebo	6 months	Hamilton Anxiety scale (HAMA), State-Trait Anxiety Inventory (STAI)	Significant improvement of anxiety in both groups without significant intergroup differences
Baksu (2009) [4]	RCT	132 healthy hysterectomized postmenopausal women	Mean age 49.4–50.9 yrs, mean BMI 26.4–27.1 kg/m2	- oCEE 0.625 mg/d - Intranasal E2 300 µg/d - tE2 gel 1.5 mg/d - No treatment (controls)	1 yr.	Hamilton Anxiety scale (HAMA)	Anxiety significantly improved in all ET groups, but significantly worsened in controls
Andreen (2006) [5]	PC-RCT with cross-over design	43 healthy symptomatic postmenopausal women	Mean age 53 yrs, mean BMI 25 kg/m2	oE2 2 mg/d + sequential - oMP 30 mg/d (1 month) - oMP 60 mg/d (1 month) - oMP 200 mg/d (1 month) - Placebo (1 month)	4 months	Modified Cyclicity Diagnoser Scale	Anxiety significantly improved with EPT containing oMP 60 mg/d compared to ET phase; with EPT containing oMP 30 mg significantly more negative mood symptoms; with EPT containing oMP 200 mg significantly more negative physical symptoms
Björn (2006) [6]	RCT (sub-study)	125 symptomatic postmenopausal women with or without a history of premenstrual syndrome	Mean age 51.8 yrs	- oE2V + sequential MPA 10 mg/d	2 months	Cyclicity Diagnoser Scale	Women with a history of premenstrual syndrome had higher scores of anxiety during the EPT compared to ET phase
Heikkinen (2006) [7]	RCT	419 postmenopausal women (at study end 176 women)	BL data of women that continued that study after the end of year 7: Mean age 56.2 yrs, mean BMI 25.3 kg/m2, mean duration of HRT 8.3 yrs	- oE2V 1 mg/d + MPA 2.5 mg/d - oE2V 1 mg/d + MPA 5 mg/d - oE2V 2 mg/d + MPA 2.5 mg/d - oE2V 2 mg/d + MPA 5 mg/d	10 yrs (9 yrs with HRT + 1 yr. without HRT)	Modified Raitasalo-Beck Depression Inventory	The degree of anxiety improved in all women from BL to year 1 and this was maintained until year 9 (no significance levels presented)
Cagnacci (2004) [8]	PC-RCT	120 postmenopausal women	Mean age 50.7–51.2 yrs, mean BMI 25.5–26.9 kg/m2	- tE2 patch 50 µg/d + sequential DYD 10 mg/d - tE2 patch 50 µg/d + sequential MPA 10 mg/d - tE2 patch 50 µg/d + sequential NMG 5 mg/d - tE2 patch 50 µg/d + sequential NETA 10 mg/d - tE2 patch 50 µg/d + Placebo (controls)	5 months	State-Trait Anxiety Inventory (STAI)	ET had no impact on anxiety, EPT containing DYD or MPA significantly improved anxiety compared to ET
Gambacciani (2003) [9]	RCT	50 healthy postmenopausal women	Mean age 54 yrs, normal mean BMI,	- oE2 1 mg/d + NETA 0.5 mg/d - Controls	3 months	Women's Health questionnaire (WHQ)	HRT significantly improved anxiety compared to BL and controls
Paoletti (2001) [10]	PC-RCT	60 healthy postmenopausal women	Mean age 52.3 yrs, at BL no psychological or mood disturbances	- tE2 patch 50 µg/d	3 months	SCL-90	E2 and E2V + CPA significantly decreased anxiety in postmenopausal

(*continued on next page*)

Table 8 (*continued*)

Author (year)	Study design	Study cohort (n)	Study cohort characteristics	Intervention	Duration of follow-up	Tool to assess anxiety	Results
				- oE2V 2 mg/d + sequential CPA 1 mg/d - No treatment			women but no difference in untreated women
Klaiber (1997) [11]	PC-RCT with cross-over design	38 healthy postmenopausal women (n = 17 early postmenopause, n = 21 late postmenopause)	Mean age 53.3 yrs, at BL no major psychiatric diseases or psychotropic drugs	Placebo – oral estropipate 1.5 mg/d + sequential NET 1 mg/d (2 months) – placebo	5 months	Profile of Mood States (POMS)	In early postmenopausal women ET and EPT significantly improved anxiety compared to placebo; in late postmenopausal women ET also significantly improved anxiety compared to placebo while EPT significantly worsened anxiety compared to placebo
Thomson & Oswald (1977) [12]	PC-RCT	34 symptomatic perimenopausal women	Mean age 48.5–49.7 yrs	- Oral piperazine estrone sulphate 3 mg/d - Placebo	2 months	Hamilton Anxiety scale (HAMA), visual analogue scale	Anxiety significantly improved in both groups without significant intergroup differences
Gülseren (2005) [13]	Prospective cohort study	42 healthy postmenopausal women	Mean age 48 yrs	- Tibolone 2.5 mg/d - No treatment (controls)	6 months	Hamilton Anxiety scale (HAMA),	Anxiety significantly improved with tibolone but not in controls
Cagnacci (1999) [14]	Prospective cohort study	62 postmenopausal women with significant psychological discomfort	Mean age 51.2–55.1 yrs	- tE2 patch 50 µg/d + sequential MPA 5 mg/d - Vaginal estriol 0.5 mg twice a week - No treatment (controls)	1 yr.	Symptom Rating Scale (SRT)	Anxiety significantly decreased in women with EPT, vaginal estriol and no treatment; anxiety decline was significantly stronger in women with EPT compared to untreated controls
Siddle (1990) [15]	Prospective cohort study	16 symptomatic postmenopausal women	Not presented	oCEE 1.25 mg/d (9 months) + sequential DYD 10 mg/d (3 months), then 20 mg/d (3 months)	9 months	Modified Leeds Scale, a 31-item symptom questionnaire	CEE significantly improved anxiety, no significant differences between ET and EPT or DYD dosages in EPT
Fitzpatrick (2000) [16]	Cross-sectional study	176 (mostly) healthy postmenopausal women	All women had used EPT containing MPA before and were switched to EPT containing MP due to MPA side effects	EPT containing oMP 100–400 mg/d for 1–6 months	Not applicable	Greene Climacteric Scale (GCS), Women's Health questionnaire (WHQ)	Significant improvement of anxiety with EPT with MP compared to EPT with MPA (GCS, WHQ)

Abbreviations: BL = baseline, BMI = body mass index, CEE = conjugated equine estrogens, CPA = cyproterone acetate, d = day, DYD = dydrogesterone, E2 = estradiol, E2V = estradiol valerate, EPT = estrogen-progestogen therapy, ET = estrogen-only therapy, MP = micronized progesterone, MPA = medroxyprogesterone acetate, NET(A) = norethindrone (acetate), NMG = nomegestrol acetate, o = oral, PC-RCT = placebo-controlled randomized-controlled trial, t = transdermal, yrs = years,

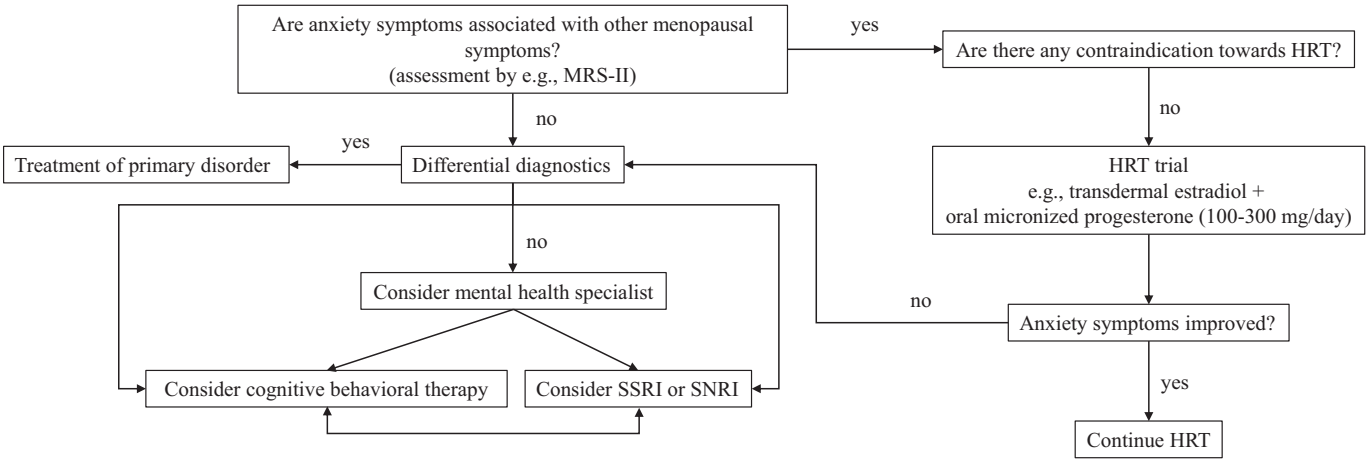

Fig. 1. Assessment and management of anxiety during the MT, modified according to [62]. Abbreviations: HRT = hormone replacement therapy, MRS = Menopause Rating Scale, SNRI = serotonin-norepinephrine reuptake inhibitors.

one option.

5.2. Limitations

This review must be considered in line of its limitations. First, although stress symptoms are omnipresent in menopausal women they are not part of routine menopause assessment and not an indication for HRT. Thus, a systematic literature search on stress and HRT did not appear helpful as it was for anxiety (disorder) symptoms. Secondly, worldwide health care systems including reimbursement for medical care differ. Thus, we are aware that the proposed management might not be implementable in all countries. Furthermore, the validated questionnaires presented may not be available in all languages which will reduce the usability in some countries.

5.3. Research agenda

There is need for more RCT's that investigate the effect of interventions targeting stress and anxiety, specifically in women in the MT. With regard to anxiety, more research is needed, covering the presentation and treatment of diffuse anxiety (symptoms not reaching any anxiety disorder cut-off) in menopausal women.

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