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Management of depressive symptoms in peri- and postmenopausal women: EMAS position statement

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ABSTRACT

Introduction: Globally, the total number of people with depression exceeds 300 million, and the incidence rate is 70 % greater in women. The perimenopause is considered to be a time of increased risk for the development of depressive symptoms and major depressive episodes.

Aim: The aim of this position statement is to provide a comprehensive model of care for the management of depressive symptoms in perimenopausal and early menopausal women, including diagnosis, treatment and follow-up. The model integrates the care provided by all those involved in the management of mild or moderate depression in midlife women.

Materials and methods: Literature review and consensus of expert opinion.

Summary recommendations: Awareness of depressive symptoms, early detection, standardized diagnostic procedures, personalized treatment and a suitable follow-up schedule need to be integrated into healthcare systems worldwide. Recommended treatment comprises antidepressants, psychosocial therapies and lifestyle changes. Alternative and complementary therapies, although widely used, may help with depression, but a stronger evidence base is needed. Although not approved for this indication, menopausal hormone therapy may improve depressive symptoms in peri- but not in postmenopausal women, especially in those with vasomotor symptoms.

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1. Introduction

The European Menopause and Andropause Society (EMAS) aims to provide holistic consensus advice on the clinical management of menopausal women through its position statements and clinical guides [1]. EMAS's healthcare model for healthy menopause covers physical, psychological and social functioning, and incorporates disability and disease [2]. This position statement sets out a model of care for the management of depressive symptoms and depressive episodes in peri- and postmenopausal women, integrating services provided by healthcare and allied professionals. It suggests how to optimize the management of depressive symptoms in perimenopausal and early menopausal women, from assessment to intervention, and covers menopausal hormone therapy (MHT), antidepressants, psychotherapy, and complementary and alternative medicines.

2. Definition and prevalence of depression

Depression represents a group of heterogeneous disorders that share phenotypic similarities and that present along a continuum of severity [3]. According to the ICD-10 classification, depressive disorders are psychopathological syndromes within the category "mood disorders" (F30-F39). Depressive disorders have high comorbidity both with other mental syndromes (e.g. anxiety, eating disorders, various psychoses) [4] and with medical disorders (e.g. endocrine illness, cardiovascular disease, cancer) [5,6]. Globally, the total number of people with depression was estimated to exceed 300 million in 2015 [7]. According to the World Health Organization (WHO), years lived with disability attributable to depression are estimated at 738/100,000 people, ranking it first in these terms (7.5.% of years lived with disability) [7]. The lifetime prevalence of any type of depression across geographic locations ranges from 1 to 17 % [8]. It has been suggested that longitudinal follow-up may reveal an even higher prevalence [9]. The incidence of depression is 70 % greater in women [10]. Furthermore, in women, depressive symptoms can be more severe and more frequent [11], and relapse risk is higher [12]. Comorbidity with medical conditions increases chronicity as well as the severity of the medical condition and is associated with increased patient malaise and dysphoria [13]. Also, the majority of depressive episodes are associated with adverse life events and/or chronic psychosocial stress [14].

Hormonal changes, such as the menopausal transition, have been found to increase the risk of a new-onset depressive episode in most [15–18] but not all studies [19]. Furthermore, the majority of perimenopausal women who develop a major depressive episode have had a previous mood episode [20].

In a within-woman, eight-year, longitudinal study to determine risk factors for depressive disorders, a diagnosis of depression was 2.5 times more likely to occur in the menopausal transition than when the woman was premenopausal [21]. After the menopause, the risk decreases. A systematic review and meta-analysis concluded that age at menopause has an impact [22]. Thus, older age at menopause was associated with a lower risk of depression in later life. Menopause at age 40 or more compared with premature menopause was associated with a 50 % decreased risk of depression (3033 unique participants; 4 studies). Furthermore, a history of depression is associated with an earlier onset of menopause [23]. In addition, in women with a history of bipolar disorder, there is an increased likelihood of mood episode exacerbation in late menopause transition and early postmenopause [24].

3. Assessment and diagnosis of depression

The menopausal transition is associated with developmental tasks or challenges such as coping with aging in general, including changes in body image, sexuality, and fitness; there are also challenges related to social and gender roles, changing relationships and family structures, and maintaining professional positions. These inherent life-phase stressors have the potential to increase the risk of feeling overwhelmed, and of losing self-esteem and general motivation, which all contribute to clinical depression. During the menopause, depression commonly presents in combination with vasomotor symptoms such as hot flushes and night sweats, leading to disturbed sleep and insomnia [25]. These other complaints may cause difficulties in diagnosing depression correctly [26]. Menopausal women with vasomotor or other symptoms usually present in primary care or to gynecologists. Risk factors for depression should be noted [27]. They include internal factors (genetics, neuroticism, low self-esteem, anxiety disorder, history of depression), external factors (substance misuse, conduct disorder) and adversity (trauma during childhood or adulthood, stressful life events in the past year, parental loss, history of divorce, marital problems, low social support, low education).

While screening with self-report questionnaires has emerged as an approach to aid in identifying women who may have depression but who do not yet have a diagnosis, clinical practice guidelines differ between countries [26,28–31]. Psychiatric history, and careful delineation of symptoms may assist in differentiating mood swings commonly experienced during the menopause transition from true depression or bipolar disorder [32,33]. In diagnosis, primary depression needs to be differentiated from secondary depression, arising in the context of a medical condition or certain drug therapies.

Thus, the assessment of menopausal women who appear to be depressed should comprise a full medical and psychiatric history, family history, social history, physical examination, and, if indicated, focused laboratory tests [34]. The stage of menopause should be established. Individual life stressors should be assessed and their impact on the emotional symptoms elucidated. Consultation with a psychiatrist or mental healthcare team should be undertaken according to local guidelines, especially if there are concerns about suicide risk [26], (Fig. 1).

4. Treatment of depression

In this section, the basic principles of management are first described, before an integrated model of care for depression management in peri- and postmenopausal women is set out, which can be adapted to individual healthcare systems. Specific interventions are considered in turn.

4.1. Basic principles

Depression may become a recurring condition. The risk of relapse and recurrence increases with each successive episode [35]. Length of maintenance treatment after remission of the acute episode and efficacy of treatment are paramount in this respect. Incomplete remission and inadequate time of maintenance pharmacotherapy are both associated with an increased risk of relapse and recurrence [12]. Complete remission is defined as a return to the premorbid level of functioning [36]. Depression is associated, in addition, with medical morbidities such as insulin resistance, osteoporosis [37], cardiovascular events [38], immune compromise [39], and lengthier recovery from medical illness [40]. Thus, there is a need to integrate the care of women with one of the medical morbidities listed with mental health services.

Treatment goals are to reduce depressive symptoms in the short term, prevent recurrence, and restore psychosocial functioning. Maintenance therapy has been shown to reduce the risk of recurrence by up to 70 % [41].

4.2. Integrated care model for depression management in menopausal women

Optimal treatment requires awareness of depressive symptoms, early detection, standardized diagnostic procedures, a personalized approach and a suitable follow-up schedule. However, healthcare

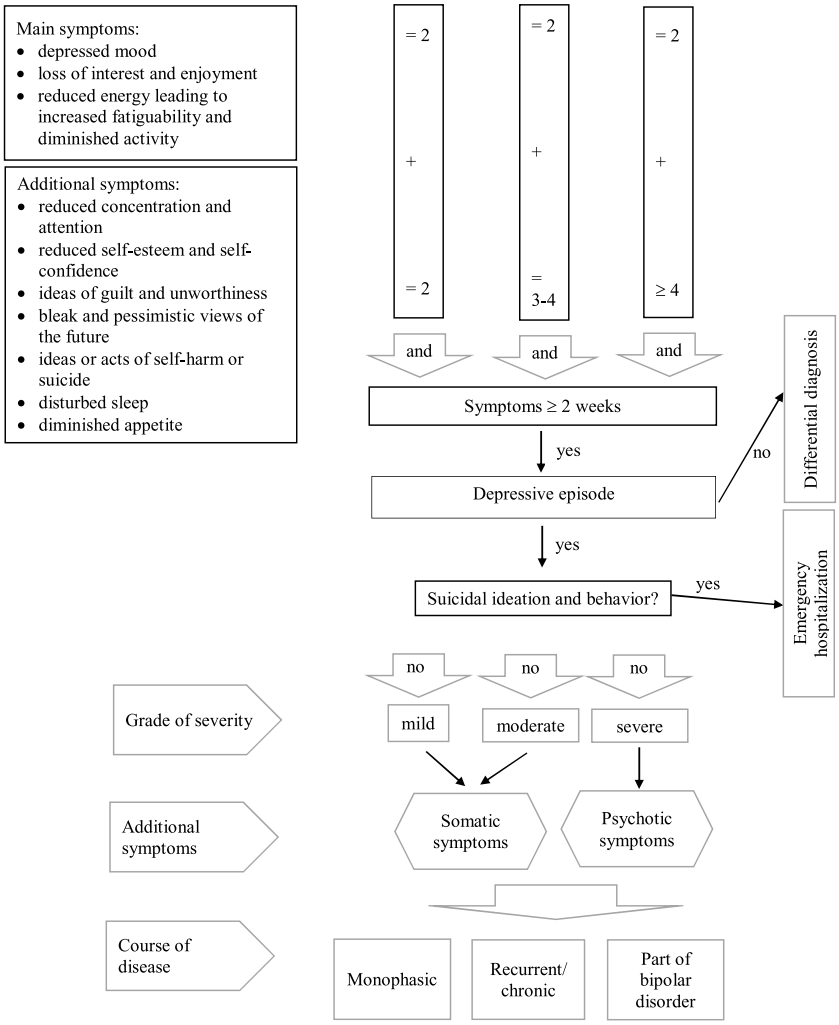

Fig. 1. Diagnostic criteria for depression and severity grades.

systems differ worldwide. The vast majority of people with depression are treated in primary care. Furthermore, primary care providers have an important role in managing chronic physical comorbidities, tackling social vulnerabilities and monitoring psychiatric risk [42].

Psychoeducation and shared decision making are the first steps in depression management, regardless of its severity. Psychoeducation is an evidence-based therapeutic intervention for patients and their families that provides information and support to better understand and cope with a disease. In depression management, psychoeducation has been found to improve the patient's prognosis and to reduce psychosocial burden for family members [43]. Follow-up should be undertaken in accordance with local guidelines and healthcare resources [42], (Fig. 2).

4.3. Treatment options for depression

Treatment options range from supportive non-drug treatments to specialized psychotherapy or pharmacotherapy. Supportive strategies include "watchful waiting", regular exercise, psychoeducation, supportive community therapy, and various naturopathic treatments. Although these may improve depressive symptoms, one must remember that the placebo effect for depression exceeds 30 % and that supportive strategies are useful only for mild depression, or as adjuvant therapies with specialized psychotherapy or pharmacotherapy. With increasing symptom severity, cognitive-behavioral therapy, interpersonal therapy and problem-solving therapy are specialized modalities that offer benefit of comparable magnitude [44]. For patients who have no access to or wish for psychotherapy, or who present with moderate to severe depression, antidepressant pharmacotherapy should be offered. Non-pharmacological biological brain stimulation, such as transcranial magnetic stimulation, electroconvulsive therapy, vagal nerve stimulation or deep brain stimulation, is usually reserved for severe refractory depression and should be administered only in specialist centers.

Primary care providers should consult with or refer to mental health specialists if in doubt, as depression management can be complex. The following sections will examine pharmacotherapy, including MHT and antidepressants, psychotherapy, complementary and alternative medicine options, notably herbal treatment with *Hypericum perforatum* (St John's wort), and lifestyle changes for the management of mild or moderate depressive episodes. The goal of the treatment of depression is symptom remission and restoring baseline functioning [45,46].

4.3.1. Menopausal hormone therapy

MHT is not approved for the treatment of depression in either Europe or the USA because of insufficient evidence. Most studies have examined the effects of unopposed transdermal estradiol, and data on oral estrogens and progestogen/ progesterone addition are scant or inconclusive. It is therefore difficult to draw conclusions about different regimens and routes of administration. However, some studies have found that estradiol has an antidepressant effect similar to that of standard antidepressants in perimenopausal but not postmenopausal women, as detailed below. There is also some evidence that tibolone

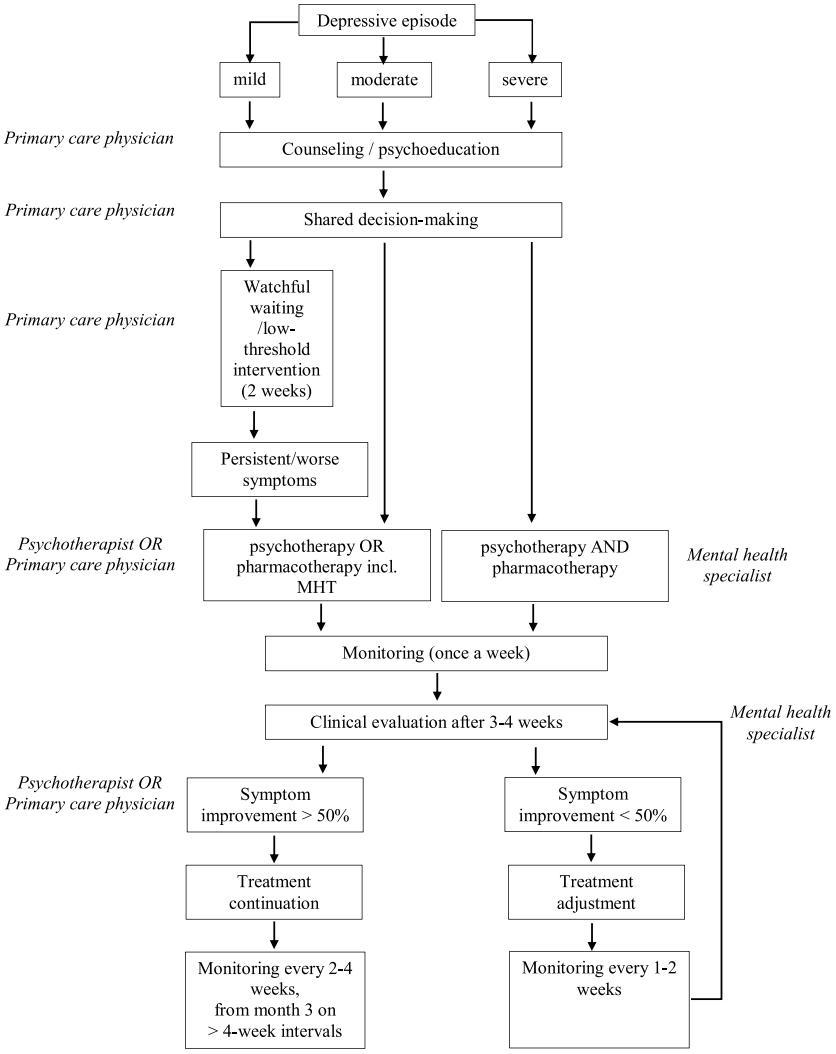

Fig. 2. Algorithm for depression management in peri- and postmenopausal women.

may be of benefit.

Vulnerability to depressed mood after estrogen withdrawal may explain the increased risk of depression during the menopause transition. One study found that blinded withdrawal of transdermal estradiol patches (100 µg /day) triggered depressive-like episodes in women with a history of perimenopausal depression [47]. An earlier report on the subject encouraged the use of transdermal estradiol patches (50 µg /day) in this context, and mood improvement seemed to be independent of vasomotor symptom amelioration [48]. In another study the beneficial effect of transdermal estradiol patches (100 µg /day) persisted for four weeks after treatment had stopped [49].

With regard to oral therapy, a study of 129 postmenopausal women with minor to major depressive episodes found that a combination of oral estradiol valerate plus dienogest improved mood compared with placebo, but the drop-out rate in both study arms was high (33 % in the MHT group and 58 % in the placebo group) [50]. Drop-out was also a concern in a pilot study that assessed hormonal adjuncts to venlafaxine and found that methyltestosterone was beneficial, but not estrogens [51]. An earlier study compared the psychological effects of two oral MHT regimens in perimenopausal women in a randomized, initially double-blind, controlled trial [52]. Thirty-eight women reporting climacteric symptoms were randomly allocated to receive either oral conjugated equine estrogen 0.625 mg daily plus progestogen (norgestrel) 150 µg for the last 12 days of each 28-day cycle, or tibolone 2.5 mg/day for 28 days. For both groups combined, there were significant improvements compared with baseline in vasomotor symptoms in the first month, and additionally in anxiety, sleep, memory and somatic dysfunction by the second and third months, but not in depression scores. However, log linear analysis showed that weekly depression scores were significantly related to improvement in vasomotor scores independent of type of therapy and time on MHT. The authors felt that the results supported the domino theory, which proposes that psychological improvement follows alleviation of vasomotor symptoms. In a recent 12-week randomized placebo-controlled trial of tibolone, participants in the treatment group demonstrated a significantly greater improvement in depression scores than the placebo group [53]. It should be noted that some, but not all, participants were taking antidepressants and vasomotor symptoms were not documented.

Looking at the postmenopause, a ten-week study examined whether estrogen therapy is effective in treating depressive disorders in older postmenopausal women (including women over the age of 60) [54]. It also examined whether progestogen addition was associated with a deterioration in mood [54]. Fifty-seven women were randomly assigned to receive 8 weeks of treatment with transdermal estradiol patches (100 µg /day) or placebo. All patients were then treated with medroxyprogesterone 10 mg/day for 2 weeks combined with the study patch. Depressive symptoms in the estradiol group and placebo group improved at a similar rate based on scores on the Hamilton Depression Scale (a 40 % decrease in depression score for the estradiol group vs. 44 % for the placebo group). No significant increase in depressive

Table 1
Overview of antidepressants.

Drug	Dosage [a,b]		Serum concentration (minimum level before drug intake) [ng/ml][c]	Therapeutic drug monitoring (TDM), level of recommendation [c]	Risk of adverse effects [d,e,f]							
	Usual starting dose per day [mg]	*Usual total dose per day [mg]*			*Anticholinergic effect*	*Drowsiness*	*Insomnia/ agitation*	*Orthostatic hypotension*	*QTc prolongation*	*Gastrointestinal toxicity*	*Weight gain*	*Sexual dysfunction*
Selective serotonin reuptake inhibitors (SSRI)												
Citalopram	20	20–40	50–110	recommended	none	none	slight	slight	slight	slight	slight	moderate
Escitalopram	10	10–20	15-80	recommended	none	none	slight	slight	slight	slight	slight	moderate
Fluoxetine	20	20–60	120–500	recommended	none	none	low	slight	slight	slight	slight	moderate
Fluvoxamine	50	50–200	60–230	recommended	none	slight	slight	slight	none to slight	slight	slight	moderate
Paroxetine	20	20–40	30–120	helpful	slight	slight	slight	low	none to slight	slight	low	high
Sertraline	50	50–200	10–150	recommended	none	none	low	slight	none to slight	low	slight	moderate
Serotonin-norepinephrine reuptake inhibitors (SNRI)												
Desvenlafaxine	25–50	50–100			none	none	slight	none	none	low	unknown	slight
Venlafaxine	37.5–75	75–375	100–400	recommended	none	slight	slight	none	slight	low	none to slight	moderate
Duloxetine	30–60	60–120	30–120	recommended	none	none	slight	none	none	low	none to slight	slight
Selective norepinephrine-dopamine reuptake inhibitors												
Bupropion	150	300	225–1500	helpful	none	none	low	none	slight	slight	none	none
Alpha1-receptor antagonists												
Mirtazapine	15	15–45	30–80	recommended	slight	high	none	none	slight	none	high	slight
Mianserine	30	60–120	15–70	helpful								
Serotonin modulators												
Nefazodone	200	300–600			slight	low	none	slight	none	low	none	none
Trazodone	100	200–500			none	high	none	slight (hypnotic dose), moderate (antidepressant dose)	slight (hypnotic dose); low (antidepressant dose)	slight (hypnotic dose); moderate (antidepressant dose)	none (hypnotic dose); slight (antidepressant dose)	slight
Vilazodone	10	40			none	none	low	none	none	high	none	low
Tricyclics and tetracyclics												
Amitriptyline	25	150–300	80–200	highly recommended	high	high	none	moderate	moderate	slight	high	moderate to high
Amoxapine	25	200–300			low	low	low	low	low	none	low	inadequate data
Clomipramine	25	100–250	230–450	highly recommended	high	high	slight	low	low	slight	high	high
Desipramine	25	150–300	100–300	recommended	slight	low	slight	low	moderate	none	slight	inadequate data
Doxepin	25	150–300	50–150	recommended	moderate	moderate	none	low	moderate	none	high	moderate
Imipramine	25	150–300	175–300	highly recommended	moderate	moderate	slight	high	moderate	slight	high	moderate
Maprotiline	25	100–225	75–130	recommended	low	moderate	none	low	moderate	none	low	inadequate data
Nortriptyline	25	50–150	70–170	highly recommended	low	low	none	slight	moderate	none	slight	inadequate data
Protriptyline	10	15-60			low	slight	slight	low	moderate	slight	slight	moderate to high
Trimipramine	25	150–300	150–300	recommended	high	high	slight	moderate	slight	none	high	inadequate data

(*continued on next page*)

Table 1 (*continued*)

Drug	Dosage [a,b]		Serum concentration (minimum level before drug intake) [ng/ml] [c]	Therapeutic drug monitoring (TDM), level of recommendation [c]	Risk of adverse effects [d,e,f]							
	Usual starting dose per day [mg]	*Usual total dose per day [mg]*			*Anticholinergic effect*	*Drowsiness*	*Insomnia/ agitation*	*Orthostatic hypotension*	*QTc prolongation*	*Gastrointestinal toxicity*	*Weight gain*	*Sexual dysfunction*
Monoamine oxidase inhibitors												
Iscarboxazid	10	10–40			slight	slight	low	low	none	slight	slight	high
Phenelzine	15	15–90			slight	low	slight	moderate	none	slight	low	high
Selegiline					slight	none	slight	slight	none	none	none	none
Tranylcypromine	10	30–60	≤ 50	eventually helpful	slight	slight	low	low	none	slight	slight	high

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symptoms was demonstrated with progestogen addition; however, positive affect decreased slightly with the use of combined estradiol-medroxyprogesterone compared with medroxyprogesterone combined with the placebo patch (5.8.%, p = .027). The authors concluded that estradiol cannot be considered an effective treatment for mild to moderate depression in postmenopausal women.

Only one randomized controlled trial has shown the efficacy of MHT in preventing the development of significant depressive symptoms in euthymic perimenopausal and early postmenopausal women. The trial involved 172 women randomized to transdermal estradiol patches (100 µg /day) or transdermal placebo for 12 months. Oral micronized progesterone (200 mg/day for 12 days) was also given every 3 months to women receiving active therapy, and identical placebo pills were given to women receiving transdermal placebo. Women on placebo were more likely to score > = 16 on the Center for Epidemiological Studies-Depression Scale (CES-D) during the intervention phase, compared to women assigned to active treatment (32.3.% vs 17.3.% ; odds ratio [OR], 2.5; 95 % CI, 1.1–5.7; p = 0.03). [55]. Note that while micronized progesterone prevents sleep disturbance in postmenopausal women, it is not licensed for this indication in either Europe or the USA [56].

International guidelines on MHT and depression differ. The Canadian Network for Mood and Anxiety Treatments (CANMAT) states that transdermal estrogens are recommended as second-line agents for perimenopausal women with depression who have no contraindications to MHT [57], whereas paucity of clinical evidence precludes such a recommendation for menopausal women with bipolar disorder [58]. An expert panel recruited by the North American Menopause Society (NAMS) concluded that, while estrogen therapy is not approved for the treatment of perimenopausal depression, there is evidence that it has antidepressant effects in perimenopausal women, particularly those with concomitant vasomotor symptoms [59].

The International Menopause Society (IMS) stated in the 2016 Global Consensus Statement that “quality of life, sexual function and other menopause-related complaints, such as joint and muscle pains, mood changes and sleep disturbances, may improve during MHT” [60]. Similarly, the UK NICE guidelines recommend considering MHT to alleviate low mood that arises as a result of the menopause [61]. MHT may increase or accelerate the response to selective serotonin reuptake inhibitors (SSRIs), but probably not serotonin-norepinephrine reuptake inhibitors (SNRIs), improving rates of partial remission [62–65].

4.3.2. Antidepressants

Approved antidepressants comprise SSRIs, SNRIs, atypical antidepressants, serotonin modulators, tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). Current standard practice is to initiate treatment with an SSRI but to switch to an SNRI (a “broader spectrum” antidepressant) if there is no adequate (over 50 %) response within the first month. Some may prefer to switch to another SSRI, but some older data support switching earlier rather than later [66]. Evidence supporting this practice has been challenged by a 2010 meta-analysis of three randomized controlled trials and an updated meta-analysis of four randomized controlled trials; both showed no benefit [67,68]. In addition, reproductive stage, time since menopause and MHT use have not been found to have an impact on antidepressant efficacy [69–71]. There are no randomized controlled trials of bupropion or vortioxetine, which have a different neurotransmitter profile in perimenopausal women.

In general, antidepressants are efficacious regardless of the baseline severity of the depression. Their efficacy is well documented. For example, one meta-analysis proved the superiority of fluoxetine or venlafaxine over placebo after six weeks of treatment, with remission occurring in more patients receiving the active drug than placebo (43 % versus 29 %) [72]. The rate of remission in milder depressive episodes was higher with the active drug than with placebo (50 % versus 37 % of patients). The rate of remission in more severe depressive episodes was

also higher with the active drug than with placebo (38 % versus 25 %). Furthermore, with increasing severity of depression, the efficacy of placebo decreases. In delusional depression, the placebo effect is no more than 5 %, while a combination of an antidepressant with an antipsychotic or with electroconvulsive therapy has an 80 % remission rate. In this particular clinical scenario, the evidence thus favors a combination of antidepressants with an antipsychotic, although, at the moment, no particular agents can be recommended [73]. In milder depression, the efficacy of antidepressants is similar to that of psychotherapy, while in more severe episodes pharmacotherapy is superior. A combination of medication and psychotherapy is superior to either alone, and psychotherapy is especially useful in the prevention of relapse. A recent systematic review and network meta-analysis of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder has underlined variability in efficacy and acceptability in head-to-head trials [74]. However, in the absence of models that can predict efficacy in individual patients, drug choice remains based upon clinically judged parameters such as safety, side-effect profile, specific depressive symptoms, comorbid symptoms, concurrent medications and patient preference (Table 1).

In refractory depression, several strategies have been suggested to enhance the response to antidepressants. MHT has been proposed as add-on therapy for depression during the menopause. Two post-hoc analyses of randomized placebo-controlled studies of SSRIs in older women suggested that estrogens may augment antidepressant response in postmenopausal women with MDD [75,76]. In the 1997 analysis by Schneider et al. [75] a variety of MHT regimens were examined, whose components included: conjugated equine estrogens, estradiol, estropipate, transdermal estradiol, intramuscular estradiol, ethinylestradiol, estrogen/methyltestosterone, esterified estrogen and medroxyprogesterone acetate. In the 2001 analysis by the same authors [76] the women had all taken unopposed estrogen (oral or vaginal conjugated equine estrogens, transdermal estradiol, esterified estrogens). However, others have failed to find any differences between MHT users and non-users in terms of response or remission rates in peri- or postmenopausal depressed women treated with SSRIs. For example, a retrospective study found that MHT consisting of conjugated estrogens with or without medroxyprogesterone acetate did not increase the efficacy of fluoxetine [77]. Furthermore, the STAR*D study found that the outcome of citalopram treatment was unaffected by unspecified MHT regimens [78]. In conclusion, further research is required in adequately powered long-term studies with defined MHT regimens.

4.3.3. Psychotherapy

A recent re-analysis shows that psychotherapy, in general, is useful for depression [79]. This also holds for patients in primary care [80]. Brief and cost-effective approaches such as cognitive-behavior therapy (CBT), problem-solving therapy and interpersonal therapy (IPT) are the most documented approaches. Psychotherapy is effective even in the elderly and in hospitalized patients. It is particularly useful in mild to moderate depression. In combination with pharmacotherapy, psychotherapy shows good results in severe depression. It has a key role in preventing new episodes [81]. Its effectiveness is reduced in severe depression because patients are too ill to engage with psychotherapy without the aid of medication. Severe depression has classically been primarily treated with antidepressants instead of psychotherapy. However, this notion has been challenged by a meta-analysis of individual patient data for a total of 1700 patients [82]. Here, the baseline severity of the depression did not affect response or remission to CBT or pharmacotherapy. CBT teaches depressed patients how to identify negative patterns of thinking and to try to replace them with healthier, positive ideas [83]. IPT focuses on difficulties within relationships, particularly interpersonal conflict and problems in social interactions, either caused by depression or responsible for it [84]. The effects of these psychotherapies have been shown to persist for a year or more after treatment, whereas antidepressants work only while they are being taken. The preference expressed by patients for psychological interventions, their efficacy (in particular in combination with antidepressants) and their comparative safety suggest that the combination of treatment methods might be the optimal strategy for managing major depressive disorder [85]. However, in practice, lack of availability of psychotherapy limits its widespread use [86].

4.3.4. Complementary and alternative medicine (CAM)

Despite a lack of evidence from randomized controlled trials, many menopausal women use CAM in the belief that these options are safer and ‘more natural’ [87]. At least one in two women use herbal treatments and dietary supplements (mostly based on phytoestrogens), regular exercise, yoga, acupuncture, meditation and so on [87–89]. There are, nevertheless, concerns about safety, such as liver toxicity, herb-drug interactions and the fact that botanical and other dietary supplements can interact with each other [see for example [90]]. Interaction of herbal treatments and dietary supplements with warfarin and aspirin can lead to bleeding. In addition, there are concerns about quality control in their production. Some products have been found to be contaminated with unlabeled ingredients such as conventional medicines (steroids), banned substances, or heavy metals; furthermore, some do not actually contain all the ingredients listed on the label. Some botanicals have estrogenic properties and should not be used by women with hormone-dependent disease such as breast cancer.

4.3.4.1. Hypericum perforatum (St. John's wort). *Hypericum perforatum* (St John's wort), whose chemical components are similar to SSRIs, is superior to placebo and comparable to standard antidepressants, but with superior tolerability [91–93]. However, efficacy seems to be restricted to mild and moderate depression (not more severe disease). Internationally, guidelines on depression management differ regarding *Hypericum perforatum*. This is due to non-standardization of the preparations and different regulations worldwide for food supplements versus approved pharmacotherapy. For example, practice guidelines from the UK National Institute for Health and Care Excellence recommend against St John’s wort for the initial treatment of major depression [94,95]. In contrast, the German S3 guideline (S3 indicates the highest level of scientific evidence) mentions St John’s wort as one treatment option for mild or moderate depression [96]. While *Hypericum perforatum* can be taken with MHT, combination with an SSRI should be avoided as it can cause serotonin syndrome [94,97]. Furthermore, St John’s wort interacts with the cytochrome CYP-450 liver enzyme system and may result in altered therapeutic levels of drugs metabolized by this pathway, such as cyclosporin, midazolam, amitriptyline and warfarin.

4.3.4.2. Melatonin. Melatonin is licensed as monotherapy for the short-term treatment of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over, but not for depression [see for example [98]]. It is also available in preparations which are unlicensed as medicinal products, but here there would be concerns about quality control of production. Treatment with melatonin [99,100] improves sleep disturbance during the menopause, and disturbed sleep has been suggested to be a risk factor for the development of depression during the menopause [101]. Furthermore, melatonin levels fall during the perimenopause, and its prescription to 43- to 49-year-old women decreases physical menopausal complaints such as fatigue [100,102]. However, a recent systematic review of randomized trials in patients with mood disorders that compared melatonin with placebo found no benefit [103]. Studies of melatonin in perimenopausal major depression are lacking.

4.3.4.3. Dietary supplements. Soybean isoflavones may have a positive impact on depression. Several studies from China and Japan have found an inverse relation between soy intake and risk of depression, although there are concerns about trial design [104]. Two trials in which

depressive symptoms were a primary outcome found that isoflavones significantly improved symptoms [105,106]. It has also been suggested that isoflavones augment the benefits of SSRIs in depressed participants, especially the combination of sertraline and isoflavones [106].

4.3.5. Lifestyle modification

Lifestyle changes may also have mood-regulatory effects. Thus, the Royal Australian and New Zealand College of Psychiatrists recommends that alongside or before prescribing any form of treatment, consideration should be given to the implementation of strategies to manage stress, ensure appropriate sleep hygiene and enable uptake of healthy lifestyle changes [107]. The European Psychiatric Association has published guidance on physical activity as a treatment for severe mental illness [108].

A meta-analysis of eleven publications concluded that low- to moderate-intensity exercises reduced depressive symptoms in midlife and older women [109]. Oxidative stress, inflammatory cytokines, neurotrophins and neurogenesis are thought to be among key pathways through which exercise exerts its beneficial effect on mood disorders [110].

Dietary factors and inflammation markers have been shown to play a role in the development of depression. The association between the dietary inflammatory index (DII), which was developed specifically to measure the inflammatory potential of diet, and risk of depression was examined in the middle-aged cohort of the Australian Longitudinal Study on Women's Health. Women with the most anti-inflammatory diet had an approximately 20 % lower risk of developing depression compared with women with the most pro-inflammatory diet [111]. Consumption of sweetened and refined foods and pastries has been shown to have a positive association with the risk of depression. The Women's Health Initiative Observational Study looked at the relationship between dietary glycemic index, glycemic load and other carbohydrates (glucose, sucrose, lactose, fructose, starch) and depression in postmenopausal women. A positive association was found between depression and progressively higher dietary glycemic index, added sugars and increased consumption of refined grain [112]. On the other hand, greater consumption of lactose, fiber, fruits (not in the form of juice) and vegetables was significantly associated with lower odds of incident depression.

5. Conclusions and recommendations

The menopausal transition is associated with an increased risk for new-onset depression and recurrence of previous depressive disorder. Management should be undertaken according to local guidelines regarding delivery of mental healthcare and it should incorporate the various therapeutic options. Approved pharmacotherapy comprises antidepressants, and in some countries also St John's wort. There is some evidence that MHT improves depressive symptoms. While MHT is not approved for depression management, it may be considered in depressed perimenopausal women if there are no contraindications.

Contributor

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