

# Low mood and depressive symptoms during perimenopause – Should General Practitioners prescribe hormone replacement therapy or antidepressants as the first-line treatment?

Post Reproductive Health

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## Abstract

Perimenopausal women have an increased risk of developing new onset and recurrent mental health conditions such as anxiety, low mood and depressive symptoms. General Practitioners frequently prescribe antidepressants as the first-line treatment for these symptoms, despite clear lack of evidence for their efficacy and their unfavourable side effect profile. This article, written by a General Practitioner, gives a practical overview of the mental health symptoms which women may report to their General Practitioners during the menopausal transition and discusses underlying causes, assessment, risk factors and treatment options based on current evidence.

## Keywords

Antidepressants, anxiety, depression, hormone replacement therapy, menopause, perimenopause

## Perimenopause and mental health

The perimenopause is defined as the transitional period prior to menopause and features clinical, biological and endocrinological changes. The perimenopause ends 12 months after the last menstrual period.<sup>1</sup> The median age of onset of perimenopausal symptoms is 47.5 years.<sup>2</sup> The average duration of the menopause transition is four years (defined by menstrual cycle irregularity), but the individual variation for this phase ranges from 0–11 years.<sup>3</sup>

The risk of depression increases during the menopause transition.<sup>4</sup> In my own clinical practice as a General Practitioner (GP), I find that from the age of 40 onwards, even while periods are still regular, women may experience a variety of different mental health symptoms. These symptoms may be new and out of character, or they may be recurrent, or cyclical, such as exacerbated perimenstrual syndrome (PMS). Heightened anxiety, tearfulness, loss of confidence, low mood or mood swings are common symptoms perimenopausal women report in my day-to-day practice. Many women report that they don't feel continuously depressed as such, but that they 'just don't feel

like themselves anymore and don't recognise the person they have become'. These mental health symptoms during the menopausal transition may occur with or without vasomotor symptoms (VMS). In the absence of VMS, irregular or missed periods, or in women deemed 'too young' for being menopausal, health care practitioners often don't consider hormonal changes as a causative factor and this can affect the treatment options offered to these patients.

There is evidence that episodes of depression associated with reproductive events are triggered by hormonal fluctuations. Some authors have argued that hormone modulated reproductive affective disorders such as PMS, perimenstrual dysphoric disorder (PMDD), pre/postnatal depression and climacteric depression are distinct forms of depression and could be categorised as subtypes of Reproductive Depression.<sup>5,6</sup> The term 'Reproductive Depression'

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was first introduced by Nappi et al.,<sup>7</sup> and it implies that whilst symptoms may be similar, the underlying biological mechanisms differ from other forms of depression. The term helps to acknowledge that there are types of depression which are specifically linked to the biology of the female sex and this could lead to a more individualised approach to treatment. Currently, the term 'Reproductive Depression' is not yet widely acknowledged by the medical profession and it is not included in Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM 5) or International Classification of Disease, Eleventh Revision (ICD-11).

Supporting the position that perimenopausal depression is a subtype of reproductive depression has important clinical implications for the treatment and/or prevention of perimenopausal depression.

Hormone replacement therapy (HRT) can be an effective and safe treatment for low mood that arises as a result of the menopause,<sup>8–10</sup> but a recent survey has shown that more than half of the GPs questioned prescribed antidepressants instead of HRT for the management of mood-related menopausal symptoms,<sup>11</sup> even though the NICE guidelines state that HRT and/or cognitive behavioural therapy (CBT) can be considered for low mood symptoms related to the menopause.<sup>12</sup> The incorrectly interpreted Women's Health Initiative Study (WHI) from 2002 may still be to blame for the reluctance of some health care practitioners to prescribe HRT.<sup>13</sup> A Canadian Study from 2005, which looked at changes in prescribing patterns related to HRT/antidepressants in Canada, confirmed that a significant decrease in the number of HRT prescriptions after 2002 was associated with a statistically significant increase in prescriptions for selective serotonin reuptake inhibitors (SSRIs) during the years after the WHI was published. They concluded that women who were previously prescribed HRT to control their (physical and psychological) menopausal symptoms were now given SSRIs instead.<sup>14</sup>

## Symptoms

Mental health-related symptoms during the perimenopause and the early menopausal years are common and particularly these symptoms and not necessarily VMS can be the main reason why women seek help from their GP. Epidemiological studies have shown that between 45% and 68% of perimenopausal women report elevated depressive symptoms.<sup>15</sup> In 15%–30% of perimenopausal women, symptoms are severe enough to be regarded as a depressive disorder.<sup>16</sup>

It is important that GPs have an awareness about these symptoms (Table 1) and their possible underlying causes in women in this age group. Every woman will experience this time in her life differently and every

**Table 1.** Mental health symptoms women report during the perimenopause.<sup>17–19</sup>

- 
- Mood swings and low mood
  - Low energy and fatigue
  - Feelings of guilt
  - Irritability, anger, rage
  - Low self-esteem and feeling of worthlessness
  - Reduced interest in socialising, feeling isolated
  - Increased anxiety and panic attacks
  - Disrupted sleep and insomnia
  - Lack of libido and reduced sexual enjoyment
  - Problems with memory and concentration
  - Agitation
- 

woman has a different range and severity of symptoms at a different age, before her periods stop for more than 12 months and she is postmenopausal. From my own experience as a menopause care provider, I find that women from their early 40s onwards frequently report that they feel more anxious, irritable and insecure, that they feel easily irritated, angry and that there are times when they feel like they are losing control over their life. Some women say that they feel overall less confident, less resilient to stress and that they have become indecisive and insecure for no reason. These symptoms often come and go during the day or they can last continuously for extended periods of time. Frequently, women also report that symptoms are exacerbated during the days before their period start. Depending on the severity and frequency of these symptoms, they can have a major detrimental effect on the way women function at work, on their relationship with their partner and on their family.

## Aetiology

Animal studies have shown that ovarian steroids have a direct impact on neurotransmitter system activities, including regulation of metabolic enzyme production as well as receptor and transporter protein activity. The pattern of effects of ovarian steroids on the serotonin system in humans is similar to those observed in animals. There is also evidence that reproductive steroids influence the serotonergic regulation of the hypothalamic-pituitary-adrenal (HPA) axis.<sup>3</sup> Neurobiological evidence indicates that estradiol has neuromodulatory and neuroprotective effects in the hypothalamus, amygdala and the hippocampi, which are directly relevant to mood symptomatology. Estrogen acts as a serotonergic agonist and is implicated in multiple mood regulating mechanisms in different brain regions. It increases serotonergic postsynaptic responsiveness, increases the number of serotonergic receptors and enhances serotonergic transport and

uptake.<sup>20</sup> A clinical study from 2015 demonstrated that the sudden (blinded) withdrawal of estradiol, which was given to participating perimenopausal women as a transdermal patch, precipitated depressive symptoms in those women who had a history of perimenopausal depression. The women in the control group, who also had a history of perimenopausal depression, but who continued to receive estradiol, had no recurrence of their depressive symptoms. The depression inducing effects of estradiol withdrawal in this study only affected women with a history of perimenopausal depression, which suggests that perimenopausal changes in estradiol levels can trigger depression in a susceptible subgroup of women.<sup>21</sup> Results from another clinical trial suggest that estradiol variability in the menopause transition enhances emotional sensitivity to psychosocial stress and this increased sensitivity may contribute to the development of depressed mood. These effects of estradiol fluctuation on stress sensitivity and mood appear to be independent of estradiol levels and VMS.<sup>22</sup> There is substantial evidence now that fluctuations of estradiol levels during the menopause transition trigger alterations in the HPA axis and changes in cortisol levels, which further supports the idea that perimenopausal depression is unique in its aetiology and that affected women could benefit from interventions to stabilize estradiol levels, such as HRT.<sup>23,24</sup>

### Risk factors

There are risk factors which make a subgroup of women more vulnerable to developing depressive symptoms during the perimenopause (Table 2). Women who have a history of increased sensitivity to hormonal fluctuations and to reproductive endocrine changes, such as PMS/PMDD or postnatal depression (PD), but also women with a history of oral contraceptive-induced dysphoria have a higher risk of developing depressive symptoms during the perimenopausal years.<sup>3</sup> Perimenopausal women with a history of PMS are three times more likely to report symptoms of depression during the menopausal transition compared to premenopausal women.<sup>17</sup> But even in women with no history of depression, the risk of new onset depression during the perimenopausal years is still twice as high as in premenopausal women.<sup>3</sup>

### Assessment

GPs have usually 10 min to take a history, make a diagnosis and discuss treatment options. It is not realistic to carry out a thorough mental health assessment during 10 min and often it requires several visits to enable the GP to make a diagnosis and for women to make an informed decision about the best possible

**Table 2.** Factors which increase the risk for depressive symptoms during the perimenopause.<sup>25,26</sup>

- 
- Previous depressive disorder
  - PMS/PMDD
  - Postnatal depression
  - Contraceptive-induced dysphoria
  - Previous and current treatment with SSRIs or other antidepressants
  - Severe vasomotor symptoms (VMS)
  - Sleep deprivation
  - Obesity
  - Chronic medical conditions
  - Psychosocial factors (bereavement, major stressful life event, unemployment)
  - Chronic stress
  - Smoking
  - Low socioeconomic status
- 

PMS: perimenstrual syndrome; PMDD: perimenstrual dysphoric disorder; SSRIs: selective serotonin reuptake inhibitors.

treatment option. Blood tests such as FSH levels may be considered in symptomatic women aged 40–45 and of course if premature ovarian insufficiency is suspected in women below the age of 40.<sup>27</sup> The GP should ask the patient about a history of depression including PD, PMS/PMDD, quality of sleep, periods (flooding, pain, frequency), contraception, as well as VMS (hot flushes, night sweats). Validated instruments such as the Beck Depression Inventory, Hamilton Depression Rating Scale or the Patient Health Questionnaire-9 can be used to measure and monitor the severity of depressive symptoms. The Greene Climacteric Scale is a specific assessment tool for menopausal symptoms, which includes physical as well as psychological parameters.<sup>28</sup> Another useful tool is the Meno-D questionnaire. This is a relatively new rating scale (2018), which was specifically developed and validated to assess the rate and severity of the characteristic symptoms of perimenopausal depression (Table 3). The concept of the Meno-D scale is based on a five-factor model: self; somatic; cognitive; sleep; sexual. It is designed to be used by clinicians, researchers and as a self-assessment tool for perimenopausal women. The questionnaire asks 12 questions and each question has five answer options, each graded from 0 to 4, according to severity.<sup>19</sup> Unfortunately, the paper does not provide scoring thresholds which would help to practically define normal from abnormal results. It may therefore be more useful as a symptom monitoring tool rather than a diagnostic tool.

### Treatment

Untreated depressive symptoms greatly affect the quality of life, relationships and the ability to function in

**Table 3.** Clinical areas which are assessed by the Meno-D questionnaire.<sup>19</sup>

- 
- Low energy
  - Paranoid thinking
  - Irritability (anger, rage)
  - Self-esteem
  - Isolation
  - Anxiety
  - Somatic symptoms (muscle aches, joint pain, headaches)
  - Sleep disturbance
  - Weight changes
  - Sexual interest (libido, discomfort)
  - Memory
  - Concentration
- 

the workplace. Depression is associated with an increased risk of heart disease, diabetes, osteoporosis and in the worst case, suicide.<sup>16</sup> Treatment should be personalised and tailored to each individual woman and her needs. Treatment progress needs to be monitored, and women should be reviewed frequently. A careful risk assessment and history taking prior to starting treatment is essential. Personal health beliefs, ideas, concern and expectations should be considered, and doctors should work in partnership with the patient, giving relevant evidence-based information to help women to make an informed decision about the best treatment option. Advice about healthy lifestyle measures like smoking cessation, reducing alcohol intake, healthy eating, exercise and managing stress should be included during the discussion about treatment. CBT and mindfulness-based therapies can be offered in addition to medication depending on severity and preferences.<sup>29</sup>

### *Hormone replacement therapy*

Fluctuating estradiol levels have been shown to contribute to the development of depressive symptoms and low mood during the perimenopause. Stabilising estradiol levels with HRT has been shown to be an effective treatment for mild to moderate depressive symptoms.<sup>9,30,31</sup> One recent clinical study showed that the combination of transdermal estradiol in combination with micronized progesterone helped to prevent clinically significant depressive symptoms among initially euthymic perimenopausal and early postmenopausal women.<sup>8</sup>

The NICE guidelines state that HRT should be considered as a treatment for low mood that arises as a result of the menopause. The guidelines also state, that due to lack of evidence, SSRIs or serotonin norepinephrine reuptake inhibitors (SNRIs) are not recommended to treat low mood in menopausal women who

have not been diagnosed with clinical depression.<sup>12</sup> It is important that health care professionals who are involved in the care of menopausal women are mindful to distinguish between severe major depressive episodes and less severe depressive symptoms and low mood. Women who diagnostically fulfil the criteria for major depression and clinical depression should still be treated with antidepressants as the first-line treatment.

Beyond the stabilisation of estradiol fluctuations to treat low mood, HRT is also the first choice for the treatment of VSM in woman who don't have contraindications. HRT improves overall quality of life, energy levels and sleep and it does not negatively affect libido or cause sexual dysfunction.<sup>32</sup> In addition, HRT is licenced for the prevention and treatment of osteoporosis,<sup>32,33</sup> and can help to prevent cardiovascular disease if started early enough.<sup>34</sup> HRT, preferably transdermal estradiol (gel or patch) should be offered as the first-line treatment to women with mild perimenopausal depressive symptoms.<sup>35</sup> Women with a uterus need endometrial protection when using estrogen replacement; however, many women with a history of PMS/PMDD and oral contraceptive-induced dysphoria are sensitive or even intolerant to synthetic progestins. Micronized progesterone (orally or vaginally) given continuously or cyclically or the Mirena coil (IUS) have been shown to be better tolerated than other progestogens with regard to mood-related side effects.<sup>36</sup>

### *Antidepressants*

In a large meta-analysis, antidepressants have been shown to be more efficacious than placebo in adults with major depressive disorder, but this analysis did not specifically look at perimenopausal women.<sup>37</sup> In 2018, the North American Menopause Society (NAMS) issued a consensus statement about the evaluation and treatment of perimenopausal depression. These guidelines recommend that antidepressants, CBT and other psychotherapies should remain the front-line treatments for major depressive episodes during the perimenopause, despite also stating that there is evidence that estrogen therapy has antidepressant effects of similar magnitude to that observed with classic antidepressant agents when administered to depressed perimenopausal woman with or without concomitant VMS.<sup>15</sup> The NAMS statement does not provide a treatment recommendation for less severe menopause-related depressive symptoms or low mood, but focuses on major depressive episodes. The NICE menopause guideline on the other hand does make this recommendation by stating that there is no clear evidence for SSRIs or SNRIs to ease low mood in

menopausal women who have not been diagnosed with clinical depression.<sup>12</sup>

With regard to the best choice of antidepressant, only Desvenlafaxine has been studied in two large randomised placebo controlled trials and proven efficacious in the treatment of depressed perimenopausal women. Most other antidepressants have been trialled in cohorts of younger premenopausal or older postmenopausal women.<sup>38,39</sup> Clinical trials have shown that compared to placebo, antidepressants can help to reduce the frequency of VMS<sup>40,41</sup>; however, compared to HRT they are much less effective. HRT has been shown to reduce the severity and frequency of VMS by up to 83%, whereas antidepressants reduced the severity by up to 50%.<sup>42</sup> In addition to that, only Paroxetine 7.5 mg (Brisdelle) has so far been approved by the FDA for the treatment of VMS, no other antidepressant is licenced for this purpose.<sup>43</sup>

Another very important consideration with regard to prescribing antidepressants in perimenopausal women is the unfavourable side effect profile. While HRT is licenced for the prevention and treatment of osteoporosis, SSRIs have been shown to significantly increase fracture risk in perimenopausal women if taken longer than five years.<sup>42</sup> Menopausal symptoms can last much longer than five years and the long-term use of antidepressants can further add to an already increased risk of osteoporosis in women. In addition to an increased fracture risk, antidepressants are also associated with cardiovascular side effects, gastrointestinal side effects, increased risk of suicidal behaviour during the first weeks of treatment, weight gain, headache and insomnia.<sup>45</sup> More than 50% of women who take SSRIs will experience sexual dysfunction, including low libido, anorgasmia and decreased arousal, which greatly affects quality of life.<sup>46</sup>

### *HRT in combination with antidepressants*

What needs to be taken into consideration, is the range of severity of perimenopausal mental health symptoms from mild to moderate and severe which is different for each woman. The most severe symptoms may fulfil the criteria of a major depressive episode as diagnosed according to the DSM 5 criteria.<sup>47</sup> Women are two to four times more likely to experience major depression during the perimenopausal or early postmenopausal phase.<sup>48</sup> Women who fulfil the criteria for major depression should be offered antidepressants as the first-line treatment. In addition, they can be offered HRT if they also experience other menopause-related symptoms. In women with mild to moderate low mood who don't achieve sufficient symptom control on HRT alone, antidepressants can be an important adjunct medication and there is some evidence that HRT can

augment and enhance the efficacy of some antidepressants. HRT can be added to an antidepressant and vice versa.<sup>15,17,46</sup> In women with a history of several depressive episodes, who have been stable for many years while taking antidepressants (SSRIs) and who are experiencing a worsening of depressive symptoms together with VMS, the antidepressant dosing may need to be adjusted and add-on hormone therapy should be considered.<sup>42</sup> Clinical decisions about treatment should be made on a personalised case-by-case evaluation.

## **Summary**

A growing body of research provides evidence that perimenopausal depression is a subtype of Reproductive Depression. Women with a history of depression or hormone-related mood changes seem to be particularly sensitive to perimenopausal estradiol fluctuations and have a higher risk of developing anxiety and depression. It is important that GPs have an awareness of Reproductive Depression and support women who enter and go through the menopausal transition appropriately and effectively. A thorough history of the woman's mental health, which also includes questions about the menstrual cycle, PMS, PD and side effects to hormonal contraception should be taken. Women should be given relevant information about the benefits and side effects of HRT, as well as antidepressants, so that they can make an informed decision about the best treatment option. Those women who do not have contraindications, such as breast cancer and are not diagnosed with clinical depression, should be offered HRT as the first-line treatment for low mood during the perimenopause and GPs who practice in the UK should follow the NICE guidelines. In more severe cases, such as major depressive episodes, a combination of antidepressants and adjunct HRT should be considered.

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