MENOPAUSE AND DEPRESSION

Understanding and interpreting menopausal symptoms can be difficult for GPs, especially so when depression may be obscuring the diagnosis. This article looks at the relationship between the two conditions, and considers how GPs can best navigate the possible prescribing and treatment options

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Depression is common. One in 4 women and 1 in 10 men have depression which is severe enough to require treatment.[1]

Depression is defined in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5)[2] as the presence of 5 or more defining symptoms, present for at least 2 weeks, which cause distress and impairment to function. NICE guidelines on the diagnosis of depression advise that a diagnosis can be made if there is the presence of at least 1 'core symptom' and more than 5 'defining symptoms'.[1]

The pathophysiology of depression is multifactorial and not fully understood. Familial associations have been seen but as yet there is no definite evidence of specific genes responsible.[3] Studies that induced depletion of serotonin in subjects, leading to the development of depressive symptoms, provide evidence for the monoamine deficiency theory of depression – that depression is caused by a reduction in neurotransmitters (serotonin, norepinephrine or dopamine).[3] Most established antidepressants target the monoamine system and, through inhibition of monoamine oxidase, prevent reuptake thus increasing the availability of monoamines in presynaptic neurones.

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Psychosocial stressors are another factor in the development of depression. Individuals demonstrate different responses to stress and activate the hypothalamus-pituitary-adrenal axis to varying degrees. Women appear to have greater stress responsiveness than men,[4] and it is well-known that depression is more prevalent in women than men. In addition, there are female-specific events when depression is more common, particularly perimenstrual changes, pregnancy, postnatally, and in the perimenopause.[5] These are times of sex hormone fluctuation, and evidence that oestrogen interacts with serotonin pathways may explain the development of depressive symptoms.[6]

Menopause

Menopause is a naturally-occurring event due to decreased ovarian reserve and a subsequent reduction in oestrogen production. The levels of oestrogen eventually fall too low to stimulate the endometrium, leading to cessation of menstruation. In the perimenopause however, there is significant hormonal variation daily, with oestrogen spikes higher than in pre-menopause.[7] It is thought that such fluctuation of oestrogen is responsible for symptoms in the perimenopause, in particular, vasomotor symptoms. A higher incidence of depression is seen in women who have a longer duration of the perimenopause[8] and a greater frequency of hot flushes.[9] This therefore suggests that an increased

GUIDELINE TO DEPRESSION[1]

- **Assess for the two 'core' symptoms of depression by asking:**
  - During the last month have you often been bothered by feeling down, depressed, or hopeless?
  - Do you have little interest or pleasure in doing things?
- **If either of the two 'core' symptoms have been present most days, most of the time, for at least 2 weeks, ask about:**
  - **Other typical symptoms of depression:**
    Fatigue/loss of energy.
    Worthlessness/excessive or inappropriate guilt.
    Recurrent thoughts of death, suicidal thoughts, or actual suicide attempts.
    Diminished ability to think/concentrate or indecisiveness.
    Psychomotor agitation or retardation.
    Insomnia/hypersomnia.
    Significant appetite and/or weight loss.
  - **Depression is diagnosed** if the person has at least five out of the nine symptoms listed above, with at least one of these a 'core' symptom.

Box modified from NICE Guideline Depression[1]

sensitivity to changing levels of oestrogen also produces mood symptoms in some women.[10]

When assessing a woman with low mood at the perimenopause, it is important to draw the distinction between a lady with true depression (as diagnosed using the DSM-5 criteria above), or a lady with "depressive symptoms", as this will influence the appropriate management. It can sometimes be difficult to determine, as several common symptoms associated with the perimenopause – such as fatigue, poor concentration, insomnia and low libido – are also symptoms of depression. However, enquiring about other menopausal symptoms such as night sweats, hot flushes, dry skin, hair changes and genitourinary symptoms can be helpful in distinguishing the two.

HRT

Hormone replacement therapy (HRT) should be the first line treatment for women with low mood in the perimenopause who are not diagnosed with depression, rather than antidepressants.[11] Giving continuous oestrogen stabilises fluctuating levels leading to clinical improvement of mood, particularly in women with concomitant vasomotor symptoms.[12] Transdermal oestrogen (as a patch or gel) has a better safety profile than oral oestrogen as it does not come with the increased risks of venous thromboembolism,[13,14] ischaemic stroke[13,14] and gallbladder problems,[15] which are associated with the oral route. Therefore, this should be the mode of delivery of choice for the oestrogen for the majority of women. If the woman has a desire to have oral treatment, then these small additional risks should be explained to her. Body identical oestradiol should be prescribed in preference to conjugated equine oestrogens, which are more thrombogenic[16] and contain a mixture of different hormones, including equine specific steroids which have unknown properties in humans.[17] It is worth noting that oral oestrogen causes increased sex hormone binding globulin, which then binds to circulating testosterone leading to a reduction in biologically active unbound testosterone, which can lead to reduced libido and a negative effect on mood and energy.[18]

If the woman has a uterus, then a progestogen is required to provide endometrial protection. Synthetic progestogens (e.g. norethisterone, norgestrel, levonorgestrel, medroxyprogesterone acetate and drospirenone) are reported to be associated with the development of low mood in some women, but body identical micronised progesterone is usually well tolerated with a lesser effect on mood.[19] It also comes with no increased risk of breast cancer for the first five years of use,[20] whereas synthetic progestogens have been shown to confer a small increased risk of breast cancer.[21,22] In addition, micronised progesterone has a safer cardiovascular and thromboembolic profile than synthetic progestogens.[23] Therefore, it makes sense to use micronised progesterone as the progestogen of choice. Currently the only preparation

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of micronised progesterone available in the UK is Utrogestan®, which can be used orally or vaginally (unlicensed use).[24] Patient preference and ability to comply with the HRT in two components should be considered, as combined products, e.g. combined patches, are currently only available with a synthetic progestogen component.

Testosterone, in addition to concurrent oestrogen therapy, has also been shown to have a beneficial effect on mood, energy levels and libido in women with perimenopausal depressive symptoms[25] and, provided the testosterone levels are kept in the physiological range, does not appear to cause significant side effects or adverse events.[26,27] The use of testosterone to treat menopausal symptoms is supported in the NICE guidance on menopause,[11] but there are currently no licensed products for women in the UK.

A recent trial has found that giving transdermal oestrogen and micronised progesterone in the perimenopause can reduce the risk of developing depressive symptoms in the perimenopause and in early postmenopausal women,[28] but more studies are needed to confirm this.

There will be some instances when it would not be appropriate to prescribe HRT, e.g. in a woman with a hormone-dependent breast cancer. There is evidence that antidepressants will help with vasomotor symptoms and menopausal women with anxiety, but do not improve low mood in women who are not clinically depressed.[11] The best evidence is for venlafaxine 37.5mg twice a day, citalopram 20mg daily or fluoxetine 20mg daily.[11]

In severe depression, oestrogen alone is not superior to antidepressants,[29] but some small studies have shown that it enhances their effect if given together.[30-32] Therefore, this would suggest that in women with severe depression at the time of menopause, antidepressants should be used first line, with consideration given to the concomitant use of HRT if there are other menopausal symptoms present, such as vasomotor symptoms.[11]

Additional treatment options for depressive symptoms in menopause include CBT[11,12] and lifestyle measures, such as adequate sleep, regular physical activity and relaxation exercises.[11]

Conflict of interest
None declared

References

References available online at www.bjfm.co.uk