Depression in midlife women

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Abbreviations

5-HT: Serotonin

BMI: Body Mass Index

CBT: Cognitive Behavioural Therapy

CEE: Conjugated Equine Estrogen

CES-D: Centre for Epidemiological Studies of Depression scale

CI: Confidence Interval

CVD: Cardiovascular Disease

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th edition

FSH: Follicle Stimulating Hormone

GnRH: Gonadotrophin-releasing hormone

GABA: Gamma-aminobutyric acid

HRT: Hormone Replacement Therapy

ICD-10: International Classification of Diseases, 10th Revision

IP3R: Inositol Triphosphate Receptor

KNDy: Kisspeptin, Neurokinin B, Dynorphin

KEEPS: Kronos Early Estrogen Prevention Study

LH: Luteinising Hormone

MDD: Major Depressive Disorder

MPOA: Median Preoptic Area

NKB: Neurokinin B

PET: Positron Emission Tomography

PMS: Premenstrual Syndrome

RCT: Randomised Controlled Trial

SDN: Sexually Dimorphic Nucleus

SSRI: Selective Serotonin Reuptake Inhibitors

SWAN: Study of Women's Health Across the Nation

TH: Tyrosine-hydroxylase

UK: United Kingdom

VMS: Vasomotor Symptoms

Abstract

Depression is one of the leading causes of disease-related disability in women, and they are nearly twice as likely as men to suffer from an episode of depression. The difference begins in early life and persists through to mid-life, and as such, these reproductive years have been labelled by some as a 'window of vulnerability'. The prevalence has been reported to be particularly high during the menopausal transition, but there is no consensus supporting a direct association with reproductive status. This may be partly due to methodological limitations and inconsistencies in the available studies, resulting from a large number of confounding factors. In addition, relationships between sex hormones and the neurotransmitters purported to be responsible for depression are complex. What appears to be universally accepted is that treatment, with oestrogen, for low mood in women during midlife years may be beneficial, and should be considered.

Key Words

Depression

Midlife

Sexual dimorphism

Receptor polymorphisms

Searching

All searches were conducted in PUBMED and EMBASE. The following search terms were combined using Boolean rules: depression, menopause, midlife, women. All searches were updated June 2016.

Searching of grey literature or unpublished literature was not undertaken. Papers published in languages other than English were not reviewed.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text.

Introduction

Depression is a broad and heterogenous diagnosis, with depressed mood and/or loss of pleasure in activities at the core (1). Severity is judged by the number and severity of symptoms, as well as the degree of functional impairment, however, persistent symptoms below the threshold criteria (ICD-10 and DSM-IV) can be distressing and disabling. It is one of the leading causes of disease-related disability in women (2), and they are nearly twice as likely, compared with men, to suffer from an episode of depression (3-5). This difference begins early in life (adolescence) and persists through the mid-50s (6, 7). Therefore, it would appear that women are more at risk of depression during their reproductive years.

Biological, social and psychological factors have a significant impact on the course of depression and the response to treatment, and in a recent review, Noble (8) noted that several biological processes have been thought to be involved in the predisposition of women to depression, including genetically determined vulnerability, hormonal fluctuations, and an undue sensitivity, to hormones, in brain systems that mediate depressive states. He also included psychosocial events; role-stress, victimization, sex-specific socialization, internalization coping style, and disadvantaged social status as contributors to the increased vulnerability of women to depression. Once the first episode has occurred, neither chronicity nor acute episode recurrence plays an important part in determining the higher rate of active depression among women, compared with men, in the 15-54 year age range, but the reasons behind this sex discrepancy are not entirely clear.

Depression: A definition

Symptoms of depression can be psychological, physical and/or social. Psychological symptoms may include feelings of low mood, sadness, hopelessness, low self-esteem, feelings of guilt, irritability and intolerance, a lack of motivation or interest, difficulty in making decisions, and thoughts of self-harm or suicide. Physical symptoms include changes in sleep pattern, changes in weight and appetite, unexplained aches and pains, and a lack of energy or loss of interest in sex. Social symptoms include reduced productivity at work, avoidance of social activities and friends, and difficulty with home and family life.

The Diagnostic and Statistical Manual of Mental Disorders (DSM) is published by the American Psychiatric Association and is the official diagnostic system for mental disorders in the United States. The International Classification of Diseases (ICD), used more widely in Europe, is the international standard diagnostic tool for epidemiology, health management and clinical purposes. A survey of Psychiatrists suggests that the former is of more value in research whilst the ICD is more frequently used for clinical diagnosis (9).

DSM describes major depressive disorder (MDD) as two or more major depressive episodes, characterised by depressed mood and/or loss of interest or pleasure in life activities for at least two weeks and including at least five symptoms (see below) that cause clinically significant impairment in social, work, or other important functioning almost every day.

1. Depressed mood most of the day
2. Diminished interest or pleasure in all or most activities
3. Significant unintentional weight loss or gain
4. Insomnia or sleeping too much
5. Agitation or psychomotor retardation noticed by others
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive guilt

8. Feelings of worthlessness or excessive guilt
9. Diminished ability to think or concentrate, or indecisiveness.
10. Recurrent thoughts of death

Chronic symptoms of depression not meeting criteria for a major depressive episode may represent a dysthymic disorder, which is described as depressed mood for most of the day, for more days than not, for at least 2 years, and the presence of two or more symptoms (see below) that cause clinically significant impairment in social, work, or other important areas of functioning:

1. Poor appetite or overeating
2. Insomnia or sleeping too much
3. Low energy or fatigue
4. Low self-esteem
5. Poor concentration or difficulty making decisions
6. Feelings of hopelessness

The 'window of vulnerability'

Depression in women has long been linked to the reproductive cycle and premenstrual syndrome (PMS), with associated mood disturbances, regularly recurs during the luteal phase of each menstrual (ovarian) cycle.

Absence of PMS before puberty, in pregnancy and after the menopause supports the theory that cyclical ovarian activity is important. Other reproductive events include postpartum depression and the 'baby blues', and this relationship between depression and the reproductive years has been described by Soares as a 'window of vulnerability' (10); and has

been supported by epidemiological data. It is also noted that this window may be influenced by changes in metabolism, sexuality, lifestyle, and overall health.

There may be significant psychosocial factors which may present at the time that a woman reaches menopause. There may be changes in the family structure, children leaving home, changes at work, possibly retirement. There may be additional caregiving responsibilities, for parents or in-laws, a well-known risk factor for depression. Although a single factor is unlikely to be causative, they may certainly contribute to depression.

The extent to which the risk of depression can be attributed purely to the menopause is less clear, there are supporting data (11), however, there are many methodological limitations and inconsistencies in the studies attempting to address this question; including variations in the definition of menopause as well as a lack of standardisation of psychiatric symptoms.

Indeed, some women will report symptoms of depression, but will never develop clinical depression (Major Depressive Disorder). The Harvard Study of Moods and Cycles (12), a population-based prospective study of premenopausal women with and without a lifetime history of major depression, was designed to address this. The findings demonstrated a two-fold increased risk of significant depressive symptoms in those who entered the perimenopause, compared with those women who remained premenopausal, after adjustment for age at study enrolment and history of negative life events. The increased risk for depression was somewhat greater in women with self-reported vasomotor symptoms.

The Penn Ovarian Ageing Study (13) provides evidence in support of these findings, and describes a diagnosis of depressive disorder 2½ times more likely to occur in the menopausal transition compared with when the woman was premenopausal (odds ratio, 2.50; 95% confidence interval, 1.25-5.02; *P*=.01). After adjusting for smoking, BMI, flushes, and other socioeconomic factors, within-woman change in menopausal status, increased levels of FSH

and LH, and increased variability of oestradiol, FSH, and LH around the woman's own mean levels were each significantly associated with high Centre for Epidemiological Studies of Depression scale (CES-D) scores. This provides further support for the impact of fluctuating, rather than absolute, hormone levels on the risk of depression.

The Study of Women's Health Across the Nation (SWAN) over ten years (14) addressed four questions; 1) does the menopausal transition or postmenopause render women more vulnerable to depression than does the premenopause? 2) does the risk for depression vary by race/ethnicity or by differing influences on risk by menopausal status among different ethnic groups? 3) if depression is more prevalent during or after the transition, is this due to hormonal alterations, psychological, developmental, and/or somatic change associated with the transition, midlife (more generally) or genetic vulnerability, and 4) what are the risk factors for depression during midlife and what is the impact of menopausal status on depression relative to other factors?

Women were more likely to report a high CES-D score when early perimenopausal, late perimenopausal, and postmenopausal relative to when they were premenopausal. Japanese and Hispanic women were more likely to report a high CES-D score compared with Caucasians. Significant predictors for a high CES-D score included vasomotor symptoms [OR (95% CI)1.62 (1.43–1.84)] being a current smoker, low social support, very stressful events, financial strain, a high BMI [OR (95% CI)1.01 (1.001–1.03)] (every 1 unit increased the odds by 1%), and having less than a college education. High social support was protective and reduced the odds by nearly 20% [OR (95% CI)0.81 (0.79–0.83)].

Most importantly menopausal status was associated with a two to four times increased likelihood of experiencing a major depressive episode, perimenopausal [odds ratio (OR)=2.27] or postmenopausal [odds ratio (OR) =3.57], independent of stressful life events,

hormones or vasomotor symptoms (VMS). The strongest predictor of major depression is a past history of major depression.

Interestingly, whilst cyclical ovarian activity has long thought to be a key factor in the risk of depression, SWAN demonstrated an association with testosterone only. A recent cross-sectional Australian study reported an excess of depressive symptoms during menopausal transition [direct odds ratio (OR) 1.35, 95% CI = 0.90, 2.01] and early postmenopause [direct odds ratio (OR) 1.31, 95% CI = 0.87, 1.98], but this was not significant and as such it was concluded that this excess could not be directly attributed to reproductive status (15). In support of SWAN data, a past history of depression was associated with increased odds of major depressive symptoms, as were the presence of risky alcohol use, self-reported arthritis, chronic pain, postnatal depression, and anxiety.

Anxiety

Studies on anxiety are sparse, however, women who report a history of depression and anxiety may report worse quality of life during the midlife years, independent of vasomotor symptoms and sleep disturbance (16). From SWAN, Bromberger described a surge in anxiety during late perimenopause, in those women without a history of anxiety. VMS were strongly associated with the occurrence of anxiety (17) both in women with and without a history of anxiety at the start of the follow-up.

In Soares review (10), 3 randomised controlled trials (RCTs) were identified, and all failed to show any beneficial effects of HRT on anxiety symptoms, however it is noted that this may be explained, in part, by low anxiety scores on entry to the study.

Sleep disturbance

Women often complain of difficulties initiating and/or maintaining sleep during the menopausal transition. It is difficult to determine whether this is a primary disorder or whether it may be related to underlying vasomotor symptoms, or depression. It may also be related to coexistent medical conditions, or lifestyle. Obstructive sleep apnoea and restless leg syndrome, are also common sleep problems in this age group, and as such can also worsen the sleep quality (18).

Possible interactions between menopause changes and sleep disturbance have been investigated, and menopausal transition was associated with the onset of sleep disturbances (19). There have been studies which have shown that it is in fact VMS that are the primary predictor of sleep problems in menopausal women (20), however, whilst sleep disturbance has been shown to be associated with depression in midlife women when compared with their non-depressed contemporaries, and there was worse sleep quality in those with VMS who were depressed, compared with those with VMS who were not depressed, there were no more nocturnal VMS, or increased number of awakenings in the depressed group (21). Therefore, in this group, the sleep disturbance does not appear to be caused by nocturnal VMS.

These findings are supported by improvements in sleep quality through the use of a sleep aid (zolpidem), with no improvement in flush number during the day, suggesting that women were actually sleeping all night with no change in nocturnal VMS.

Sexual Dimorphism

In a recent review by Panzica (22), it is noted that sexually dimorphic behaviours may be suggestive of sex differences in brain neuroanatomy and neurophysiology. Perhaps this may

in part explain why women are nearly twice as likely to suffer from an episode of depression, compared with men.

The link between gonads and differences in sexual behaviour was first demonstrated by Berthold (a German Physiologist), in 1849, during his experiments with roosters. He observed that it was not only phenotypical characteristics that were dependent on the testes, but also behaviours. Since these early experiments, anatomical differences in the hypothalamus, including a sexually dimorphic nucleus (SDN) within the median preoptic area (MPOA), with higher volumes and cell numbers in male rats compared with female rats (23, 24), and this has subsequently been described in different vertebrate species, including humans (25).

The preoptic area is responsible for reproduction, thermoregulation, and sleep, via a complex network of regulatory signals, which include neurotransmitters, neuropeptides and hormones. Serotonin (5-HT) is one of these neurotransmitters and may be involved in thermoregulation as well as sleep and release of gonadotrophin-releasing hormone (GnRH). Changes in 5-HT receptors and transporters are reported in aging, and animal studies have reported that these preoptic neurons are affected during reproductive aging (26). Further work would be needed to determine whether this may play a role in the pathophysiology of depression during reproductive aging in humans and whether sexual dimorphism in this area can explain the differences seen in men and women.

Gonadal steroids, oestradiol and progesterone have also been shown to have an effect on gamma-aminobutyric acid (GABA), as well as noradrenaline and serotonin, all of which are implicated in the development of depression (27). The expression of the enzyme required for GABA synthesis is sexually dimorphic in discrete regions of the hypothalamus, and also in

amygdala and the hippocampus (28). GABA also appears to be sensitive to oestradiol during the sensitive period of steroid-mediated brain sexual differentiation (29).

Brain-born oestradiol has been shown to rapidly block GABA release in females, but not in males, due to generation of inositol triphosphate and activation of its receptor (IP3R). The complexes of ERα, glutamate receptor and IP3R are present in both sexes, but are regulated by oestradiol only in females (30).

Tyrosine-hydroxylase (TH), the rate-limiting enzyme involved in dopamine synthesis, has also been shown to be sexually dimorphic, particularly in the anterior preoptic area, and the arcuate nucleus (31, 32). Recent studies have shown that at least part of these two populations of dopaminergic neurons also express kisspeptin (33).

The kisspeptin/neurokinin B/dynorphin signalling system in the hypothalamus is the key proximate stimulus to GnRH secretion: individuals with inactivating mutations in the genes encoding kisspeptin or neurokinin B or their receptors do not enter puberty (34). The kisspeptin system is another sexually dimorphic system, with higher numbers of cells and fibres in the female than in the male (33).

Kisspeptin neurones are a key locus of sex steroid feedback in the hypothalamus, and in humans, administration of kisspeptin stimulates gonadotrophin secretion in men and women, with increases in GnRH/LH pulse frequency (35). Post-mortem studies have shown hypertrophy of neurons in the hypothalamic infundibular nucleus in postmenopausal women (36) with increased NKB and kisspeptin gene expression (37). Ovariectomy resulted in similar changes in young monkeys (38), and oestrogen suppressed NKB and kisspeptin expression (39). Kisspeptin, Neurokinin B and Dynorphin (KNDy) neurones in the hypothalamus are thus obligate regulators of GnRH secretion across species, and are sensitive to oestrogen withdrawal.

Animal studies have also demonstrated some behaviour associations with kisspeptin and its receptors, including anxiety and depression (40); as the upstream regulator of GnRH in humans, and considering its complex relationship with 5-HT, alterations seen in kisspeptin in the postmenopause period may play a role in mood regulation in women during their midlife years.

Oestrogen receptor polymorphisms

Oestrogen receptors are found throughout the brain, and the effects of oestrogen can be observed in the hypothalamus, prefrontal cortex, hippocampus, and brainstem.

In animal models, withdrawal of estrogens has been proposed to play a key role in the onset of postpartum anxiety and depression, which typically occur within 4–6 weeks after birth. However, circulating estrogen levels, which are drastically reduced during the early postpartum period, return to diestrus levels by 3 weeks postpartum, raising the possibility that changes in estrogen sensitivity are involved in the postpartum response (41).

Oestrogen receptors ER-α and ER-β are transcribed from two genes, ESR1 and ESR2, respectively, and allelic variation in these two receptors, especially ESR1, has been shown to be associated with some health outcomes, i.e. breast cancer (42), high density lipoprotein cholesterol (43), and all-cause mortality (44). There has also been increasing interest in the way in which allelic variation in these genes may influence depression, suggesting that ER genes might be important in the pathophysiological mechanism of post-menopausal depression.

In humans, ERa receptor polymorphism has been shown to have an association with depression in post-menopausal women (45), and in the Nurse's Health Study (46) women

with the AA alleles of ESR2 RS4986938 had higher prevalence of lifetime major depression than women with other allele frequencies. However, the date are inconsistent, and population-based studies that have evaluated the role of allelic variation in oestrogen receptors and depression have been mixed (47).

Serotonin receptor polymorphisms

5HTT is an integral membrane protein that moves the serotonin neurotransmitter from the synaptic cleft to the presynaptic neurons. A functional serotonin-transporter-linked polymorphic region (5-HTTLPR) polymorphism is characterized by the insertion or deletion of a 44-bp fragment and, consequently, the creation of a short or a long allele. A short allele has a lower ability to uptake serotonin than a long allele. A small study examined whether the presence of a serotonin transporter polymorphism was associated with the development of depressive symptoms in late-reproductive-age women. There was no association demonstrated (48).

Tentative links

No links have been found between levels of Vitamin B12 and folate and the risk of depression in women in the midlife years (49). Neither do biomarkers of omega-3 appear to be related to risk of new depression in postmenopausal women (50), however, women with higher serum magnesium and zinc levels had fewer depressive symptoms (51), although this was a small study of only 171 women.

Treatment

There are numerous studies that have demonstrated the beneficial effects of oestrogen on mood in midlife women (52-55). The Revised Global Consensus Statement on Menopausal Hormone Therapy (56) states that "MHT (menopausal hormone therapy) may be beneficial in improving mood in early postmenopausal women with depressive and/or anxiety symptoms. MHT may also be beneficial for perimenopausal women with major depression but antidepressant therapy remains first-line treatment in this setting". Very recently published NICE guidance for Menopause (57) supports the consideration of HRT to alleviate low mood that has arisen as a result of the menopause.

Antidepressants are not routinely used to treat persistent subthreshold depressive symptoms or mild depression because the risk–benefit ratio is poor, but an SSRI may be considered in those who have not benefited from a low-intensity psychosocial intervention (1).

Oestrogen increases the synthesis and availability of 5-HT, by decreasing the activity of the enzymes involved in 5-HT degradation, monamine oxidase inhibitors A and B (58), and increases in tryptophan hydroxylase, the rate-limiting enzyme of 5-HT synthesis (59). Oestrogen also regulates 5-HT transporters, used for reuptake to the presyntatic cleft. Blocking these receptors to increase available 5-HT is the basis by which antidepressants, selective serotonin reuptake inhibitors (SSRI) and serotonin and noradrenaline reuptake inhibitors (SNRI) work in the treatment of depression. There is increased 5-HT in the synaptic cleft with oestrogen as a result of down-regulation of 5-HT1A autoreceptors and upregulation of 5-HT2A receptors (10).

Brain concentrations of progesterone and allopregnanolone are altered in animal models of anxiety and depression (60), and pharmacological treatment with antidepressants, antipsychotics and mood stabilisers restore altered central and peripheral concentrations of

allopregnanolone (61), suggesting that neuroactive steroids may contribute to the therapeutic efficacy of antidepressant medications.

PET studies of patients with depression have supported the role of serotonin in depression, however only a few studies have used PET to study the role of gonadal hormones in depression in humans. A recent study demonstrated a decrease in 5-HTT binding potential after both oestrogen alone and oestrogen + testosterone treatment compared to baseline, further supporting the role of gonadal hormones in serotonin regulated mood disorders (62).

The ancillary Cognitive and Affective Study (KEEPS-Cog) of the Kronos Early Estrogen Prevention Study (KEEPS), a randomised, double-blinded, placebo controlled clinical trial, in 9 US academic centres, demonstrated beneficial mood effects in recently postmenopausal women with 4 years of CEE, but not with 4 years of E_2 (63).

Isoflavones and red clover may improve anxiety for women with menopausal symptoms, but caution should be exercised as there is a lack of consistency between the constituents of herbal preparations, isoflavones and phytoestrogens (57).

Psychotherapy, including cognitive behavioral therapy, interpersonal therapy, and psychodynamic psychotherapy may be beneficial for some women, alone or in conjunction with prescribed antidepressants (64, 65).

Obesity and a sedentary lifestyle are associated with depressive symptoms and anxiety in women during midlife years (66) The Canadian Network for Mood and Anxiety Treatments (CANMAT) produced clinical guidelines for the management of adults with MDD, and recommended exercise, light therapy, St. John's wort, omega-3 fatty acids, SAM-e, and yoga as first- or second-line treatments for mild to moderate MDD. Adjunctive exercise and

adjunctive St. John's wort are second-line recommendations for moderate to severe MDD (67).

Is depression a risk factor for other morbidities?

Depression is associated with multiple medical conditions and symptoms, including mortality from cardiovascular disease (CVD) (68, 69), and diabetes (70), and can be both a risk factor for and a consequence of illness (14).

However, depression can be associated with lifestyle factors that can cause disease, for example, smoking, excess alcohol intake, obesity and a sedentary lifestyle. Therefore interpretation of the data can be challenging. The Million Women Study, a prospective study of UK women recruited between 1996 and 2001, demonstrated that poor health can cause unhappiness in middle-aged women, but after adjustment for potential confounders, happiness and other measures of wellbeing did not appear to have any effect on mortality (71). There was some excess mortality when adjusting only for age, but when adjusted for other measures, there was no association for all-cause mortality, ischaemic heart disease, or cancer. Interestingly, the authors suggest that whilst adjustment has been made for confounders that may affect health and mortality adversely, e.g smoking, these should perhaps be considered mediators of the unhappiness-mortality association.

Conclusion

Women in the midlife are at an increased risk of low mood and depression; however it is still not clear whether this is directly attributable to reproductive status. Whilst it is likely that this is related to the changing hormonal milieu, the complex relationships that exist between

gonadal steroids and neurotransmitters, and their receptors, mean that this pathophysiology is still poorly understood. A past history of depression seems to be the most important risk factor, but there are a number of confounding factors, not limited to, but including comorbid medical conditions, education, and hazardous lifestyle choices. What is clear is that there may be some benefit in treating low mood with oestrogen replacement, which is likely to improve vasomotor symptoms, if present, and may, as a consequence, improve associated symptoms of anxiety. CBT may be beneficial for some women, but caution must be exercised with herbal preparations, isoflavones and phytoestrogens due to inconsistencies in preparations. Above all, it is imperative that we consider all possible causes of low mood, as well as associations of depression with other co-morbidities, and aim to optimise midlife health.

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