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Mental Health Issues in Menopause

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Abstract

Menopause is an inevitable phase of life in women which comes with various physical and mental health issues. Middle age, specifically the fourth decade of life is the common age for the onset of menopause in which fluctuation in sex steroid hormones leads to physical as well as mental symptoms. Vasomotor symptoms such as hot flashes and night sweating gradually progress in the menopausal transition and last around 5-6 years after the onset. These are the earliest symptoms that have been reported by around 85% of women. More than 50% of women suffer from sleep disturbance whereas around 40% of women reported depressive symptoms while entering the menopausal phase. Anxiety disorders are quite prevalent and most of the time comorbid with depression. Common presentation is usually in the form of generalized anxiety and Panic attack symptoms. Mood swings, irritability, and anxiety symptoms are heightened in the menopausal transition. Cognitive impairment during the perimenopausal and post-menopausal phases such as disturbance in concentration and memory is very common at this age. Women with mild menopausal symptoms are advised for lifestyle modification whereas those with moderate to severe symptoms need pharmacological therapy along with lifestyle changes.

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Introduction

Permanent cessation of menstruation is known as Menopause, a normal physiological process for every woman of middle age goes through. While in the perimenopausal phase (amid menopausal progression), women may observe various symptoms such as hot flashes, dryness of the vagina, night sweats, disturbance in sleep, dysphoria, loss of libido and memory, and other cognitive deficits, etc.[1]

In their systematic review, JB Prasad et al found that the common age at menopause in India is estimated to be around 46 years, with the mean age ranging from 44.7 years to 48.9 years. Also, they attempted to exhibit a correlation between age at menarche with age at menopause i.e., later onset of menarche -the later onset of menopause.[2]

Variation in sex steroid hormones in the perimenopausal phase may have an impact on mental health pertinent to various psychiatric illnesses as it was seen that depressed women had reduced levels of estrogen than non-depressed controls.[3]

Based on the relevance of the title, we have searched various articles in the Google search engine, and various other internet platforms like PubMed by using keywords like "Menopause", "Mental health", "Mood", "Cognition", "Sleep" and "Psychiatric illness" to explore and understand the association between psychiatric symptoms and the menopausal phase from the neuroendocrinal perspective and the contribution of various psychiatric illnesses in the peri and menopausal phase.

Salient Clinical Features

Vasomotor symptoms

It is among the most common symptoms that trouble women during their menopausal progression. Although the grimness and time span of the vasomotor symptoms may alter from person to person, around 85% of women undergoing the menopausal phase reported it. Around 55% of women reported these symptoms even before the advent of menstrual irregularities, which hints at the beginning of the menopausal progression. The severity of symptoms gradually progresses over the years and reaches its summit in the late menopausal transition and then gradually starts disappearing over the next few years. The Average time span of hot flashes is around 5.2 years. However, around a quarter proportion of women may come across hot flashes more than 5 years post-menopause.[4]

Sleep Disturbance

With advancing age, sleep quality also deteriorates, and menopause seems to add to worsening of the sleep problems.[5] More than 50% of women report a reduction in sleep quality after reaching menopause. Hormonal variation during the menopausal transition significantly affects the quality of sleep, apart from advancing age.[6]
Around 23.6% of females in the age width of 45-49 years whereas about 40% of females in their early 50s reported sleep disturbance.[7]

Frequent awakenings, difficulty falling asleep, and fragmented sleep were a few common complaints reported which were associated with vasomotor symptoms. However, the direct link between cessation of ovarian function and sleep disturbance is debatable and needs further exploration.[8,9]

Mood Disorders

The sadness of mood, decreased interest, and reduced activity most of the time of the day are cardinal features for the diagnosis of depression. Apart from it, sleep disturbance, reduced self-esteem, and confidence, negative view about the future, excessive and inappropriate guilt, irritability, and ideas of self-harm which may lead to suicide many a time are the common features.[10]

The prevalence of depression in females is estimated to be around 42.47%, ranging from 28-58 years.[11]

The peak onset of the depressive episode has been reported in the fourth decade of life and the menopausal period makes women in this age range more susceptible to the onset of depression.[12] Many large cohort studies have demonstrated vulnerability to depression while undergoing a menopausal transition. There is around 3 times more risk for the development of clinical depression in women being in their pre-and post-menopausal phases.[13,14] However there is no established correlation between circulating estradiol or FSH level and depressive disorder.[15]

Various risk factors which may make women susceptible to precipitate into depressive episodes are:[16]

- Previous episode of depression
- Comorbid anxiety disorders
- Lack of quality sleep
- Distressing and adverse life events
- Higher BMI
- Smoking
- Younger age
- Job loss or retirement and
- Hormonal variation

Many midlife adverse events which may not act as an independent factor, but may contribute to developing depression in women are;

- Alterations in family structure and functioning of marriage
- Living alone after children's departure from home
- Retirement or returning to the job
- New obligations as a caregiver for parents or in-laws.[4]

Anxiety Disorders

Due to the ubiquity of anxiety disorders in females, it is important that they are evaluated for symptoms

such as panic attacks and generalized worry. The likelihood of anxiety being triggered during the menopause transition is like that of depression. In addition to mood swings and irritability, anxiety also peaked early in the transition.[17]

Although affective anxiety is known to trigger menopausal hot flashes, somatic anxiety is a more common cause of these symptoms which could be a potential treatment target. Early perimenopausal women are more prone to experiencing psychological distress than older women. Those with low anxiety levels during the premenopausal period are more likely to experience elevated levels of anxiety symptoms during the menopausal transition.[18]

Cognitive Function

Disturbance in mental clarity along with memory problems is collectively termed as "Brain fog" which makes the perimenopausal phase difficult in terms of carrying out daily life activities.[19]

Women undergoing menopausal transition may have trouble recalling names and verbally told details and possibly notice trouble carrying out executive functions. Earlier the onset of menopause, more cognitive symptoms were reported in women. Women taking hormone replacement therapy ahead of the onset of menopause performed better in memory tests in comparison to those who did not do so. Women who had a longer fertile period, which ended later naturally, were at lesser risk of developing dementia at the latter stage of life.[20,21]

The risk of development of dementia is higher in females than males of the same age group. Many studies have exhibited the role of estrogen, variation in the level or deficits of which may contribute to the development of dementia as estrogen hormone interacts with cholinergic as well as serotonergic systems essential for normal brain functioning.[22]

Sexual Dysfunction

A recent study done in 2020 in India estimated the prevalence of sexual dysfunction in females to be around 82%.[23]

The perimenopausal period is a susceptible phase that increases the chances of sexual dysfunction, as robust shreds of evidence have been found regarding it in various studies.[24,25]

The dearth of knowledge pertinent to sexual problems in females with advancing age may be due to the convoluted female sexuality which is directed by multiple factors such as physiologic, social, and emotional factors.[26,27]

The deterioration in sexual functioning is quite evident from early to late menopausal progression. The types of ordeals in sexual functioning affecting women in the menopausal transition phase are:[28,29]

- Vaginal dryness
- Painful coitus
- Decreased sexual desire, frequency, and reciprocity towards partner's sexual urge

Pathophysiology

Normally, the neuroendocrinal outflow is via the Hypothalamic - Pituitary - Gonadal axis, the Estrogen hormone increases gradually during the preovulatory phase, and then during post ovulation Progesterone hormone increases. Later, during the perimenopausal transition because of follicle reduction, the ovary no more responds to FSH and LH which ultimately hampers the synthesis of Oestrogen and Progesterone gradually and ultimately comes to halt. A transition from premenopausal to perimenopause status can be identified when women complain about increased cycle length for up to more than 7 days for two consecutive periods and/or two serially skipped menstrual cycles.[30]

The fourth decade is the age when almost all women enter the menopausal transition, which is characterized by marked alterations in menstrual cycle duration, frequency, reduced fertility, and in most of the women beginning of Vasomotor symptoms and sleep disturbances.[30,31]

Variation in ovarian hormones across life stages. Figure modified.[32]

An elevation in FSH and fluctuation in estrogen levels amid the perimenopausal transition may reflect the development of these symptoms. Progesterone, which is dependent on ovulation, becomes irregular and finally ceases once menopause is attained.[30,32]

Recently, the contribution of hypothalamic KNDy (Kisspeptin, Neurokinin B, and Dynorphin) neurons has been hypothesized. These KNDy neurons are located in the arcuate nucleus of the hypothalamus, and they are supposed to play an important role in

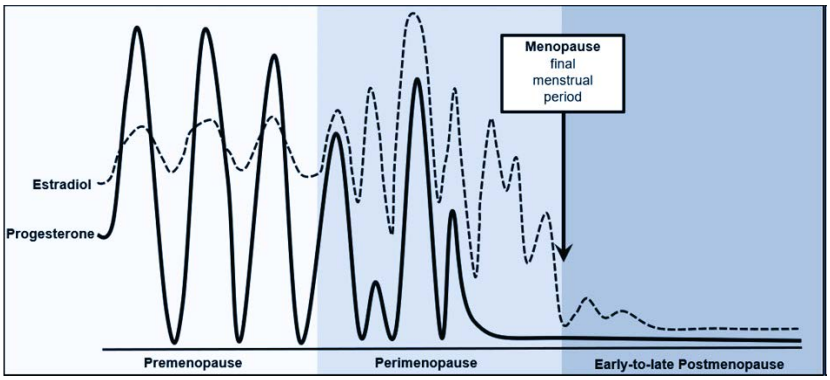

Figure 1: variation in serum levels of sex steroid hormones across reproductive lifespan[32]

the HPG axis by generating GnRH pulses. By this mechanism, KNDy neurons are assumed to control release of LH and FSH, which in turn induces estradiol. The estradiol gives negative feedback by acting on these KNDy neurons. In menopausal transition, decreased level of estradiol leads to KNDy neuronal hypertrophy. Since these KNDy neurons are projected to the MnPO (median preoptic) nucleus of the hypothalamus where they bind to NK3 (Neurokinin 3) Receptors, which results in heat dissipation causing vasomotor symptoms.[33-35]

Estrogen receptors are widely distributed in the central nervous system and are thought to play an important role in cognitive functions like memory and executive function. The two isoforms of Estrogen receptors namely Estrogen Receptor Alpha and Beta have been found important for the same. Estrogen Receptor Alpha is expressed in the nucleus basalis of Myenert while Beta isoform receptors are mostly situated in the cerebral cortex and hippocampus.[36]

Estradiol has been found to induce a trophic effect in the basal forebrain and hippocampus essential for memory and executive function.[37,38]

Management

Vasomotor Symptoms

Vasomotor symptoms are managed as per the severity.

- Symptoms are mild when they do not cause any disturbance in daily life activities.
- Moderate when symptoms cause some interference in daily activities.
- Severe when they make the person not able to perform daily activities.[39]

Women with mild Vasomotor symptoms are advised for the lifestyle modification such as:

- Refraining from alcoholic beverages, spicy food, stressful situations.
- Keeping the room temperature on the lower side
- Use of fan and sweat-friendly clothes.
- Low doses of vitamin E.
- Body weight reduction.
- Cognitive behavioral therapy.[40-42]

For moderate to severe vasomotor symptoms**,** most patients will require pharmacotherapy along with behavioral and lifestyle modification. This consists of hormonal and non-hormonal treatments.

Hormonal therapy is the mainstay treatment for women with no contraindications.[43]

- Hormonal therapy is advised for postmenopausal women depending upon the situation such that women with intact uterus require a combination of Estrogen and progesterone for protection against uterine carcinoma.
- Hysterectomized women should be prescribed estrogen only.
- Women who are diagnosed as diabetic, increased triglycerides, have vascular headaches particularly non-classical type, susceptible to venous thrombosis, gall bladder, and liver diseases are advised for transdermal therapy.
- Hormonal therapy can be used with safety for up to 3-5 years and/or till 60 years of age and after which it may be stopped by tapering off the dose over the span of 6 to 12 months.[43]

Several studies reported a substantial decrease in the frequency and extent of hot flashes with hormonal therapy.

Non-hormonal therapy is advised for those women:

- Who are not able to tolerate or are contraindicated from hormonal therapy.[44]
- Age more than 60 years or
- More than 10 years of hormonal therapy.[45]

Several non-hormonal management modalities are available which include Selective Serotonin Reuptake Inhibitors (SSRI), Serotonin Norepinephrine Reuptake Inhibitors (SNRI), Gabapentinoids, etc. The efficacy of SSRIs and SNRIs has been reported for the management of vasomotor symptoms.[46]

From several SSRIs available, Paroxetine (7.5- 25 mg per day) and Escitalopram (10-20mg per day) are preferred, while Fluoxetine and Sertraline have doubtful efficacy for the same.[47] The time taken to exhibit the desired effect in the management of vasomotor symptoms is relatively lesser than the antidepressant effect. SNRIs such as Venlafaxine and desvenlafaxine have shown equal efficacy for the management of vasomotor symptoms.[48]

Gabapentin is another option with the added benefit of sleep cycle maintenance and has efficacy equal to Venlafaxine but is preferred lesser because of relatively poor tolerability.[49] Dosing of gabapentin is based on the patient's tolerability as it causes sedation, taking this into consideration, a single dose of 100-300 mg is started at bedtime. For severe and frequent hot flashes 100mg dose is started and gradually increased for the maximum effective tolerated dose.[50]

Paroxetine is the first SSRI that is US FDA-approved to be used in moderate to severe vasomotor symptoms.[51]

Sleep Disturbances and Insomnia[52,53]

For the assessment of sleep patterns and complaints, polysomnography is a clinically significant tool that is being used. Treatment of sleep disturbance is based on the underlying causes:

For sleep apnea, continuous positive airway pressure devices are useful.

For restless leg syndrome, various dopamine agonists like Pramipexole, Ropinirole, and Rotigotine have shown their efficacy and apart from these, gabapentin was also found useful.

Primary insomnia exhibits a better response to Cognitive Behavior Therapy for Insomnia (CBT-I), Non-Benzodiazepines, and Melatonin.

- Sleep disturbance associated with depression may demonstrate a better outcome with antidepressants.

For persistent sleep disturbance, one should refer to a sleep specialist for comprehensive sleep management. Benzodiazepines are used for the symptomatic management of most sleep problems including chronic sleep disturbances.

Hormone Replacement Therapy currently does not have robust evidence in terms of efficacy in managing sleep problems in menopausal women. Regular exercise, self-hypnosis, and maintaining sleep hygiene are essential objectives for achieving good quality of sleep.

Adverse mood and anxiety disorders[54,55]

Psychotherapy and a combination of psychotherapy with antidepressants may be clinically useful first-line management modalities in Major depressive episodes. The management of depression is mostly done on a pragmatic level by considering the patient's profile such as the severity of the illness and tolerability of medicines.

Pharmacologically, SSRIs are the first-line medications for the management of depression. Various SSRIs such as Escitalopram, Fluoxetine, Paroxetine, Sertraline, and Citalopram are available. Once started, it may take around 6 to 8 weeks to demonstrate its effect on the patient.

In menopausal women, due to multiple comorbidities, there is a risk of drug interactions, and Escitalopram being a pure SSRI has a lesser risk for the same. Titration of the drug is very essential in order to avoid the side effects of SSRIs, it should be administered at low doses and gradually escalated as per the response.

Soares et al in their study regarding the comparative efficacy of SSRI and HRT found Escitalopram (SSRI) superior to the combination of Estrogen and progesterone in managing depression along with menopausal symptoms.

Cognitive impairment

Several studies have found robust evidence regarding the role of Estrogen in cognitive functions, but the relationship is yet to be simplified. The neuroprotective effect of hormone replacement therapy

is under research. In the Women's Health Initiative Memory Study (WHIMS), which was a randomized, placebo-controlled clinical trial, 65yrs age and old participants were taken. It was the first large, long-term study to address the cognitive effects of MHT (0.625 mg of conjugated equine estrogen (CEE) plus 2.5 mg of medroxyprogesterone acetate) in the prevention of AD. The results demonstrated that after a mean follow-up of 4.2 years, MHT failed to diminish the general cognitive decline in the patients.[56]

In case of minor and major cognitive impairments, it is advisable to refer to a neurologist or a geriatric psychiatrist for comprehensive management. Acetylcholine esterase inhibitors like Donepezil have exhibited a potential benefit in patients with early dementia.[54]

Atomoxetine, a Selective Norepinephrine Reuptake Inhibitor, commonly recommended in patients with attention deficit hyperactivity disorder (ADHD) has shown a convincing subjective improvement in cognitive functions, particularly in memory in menopausal women.[57]

Freeman et al did a study to estimate the efficacy of Vortioxetine in reducing vasomotor, depressive, and cognitive symptoms associated with menopausal transition and found a significant improvement posttreatment. The depression response rate was 75% and the remission rate was 70.8%. The periodicity and extent of vasomotor symptoms reduced significantly. The individuals performed well on Digit Symbol Substitution Test (DSST) but not on the Cogstate test. The internal and external validity of the results warrants further study for a robust conclusion since the sample size for the study was not large.[58]

Several lifestyle modifications which are advisable for a better quality of life are:

- Regular exercise
- Green leafy vegetables, milk, seafood, and fruits in the diet
- Engaging in regular social activities
- Participation in cognitive exercises like reading, writing, and solving crossword puzzles[4]

Sexual dysfunctions

The management of sexual dysfunction in menopausal women is based on the cause. Many problems in these age-like vasomotor symptoms, vaginal dryness, and adverse mood may contribute to impairments in sexual function, and treatment of these may, in turn, improve sexual function. Sexual dysfunction due to surgical menopause is thought to be due to a deficiency of androgens. Dehydroepiandrosterone (DHEA) and vaginal estradiol may be effective in the management of dyspareunia. Several studies suggest the use of testosterone in the treatment of various sexual dysfunction domains like decreased desire and frequency in post-menopausal women. Patients with an increased risk of endometrial hyperplasia or carcinoma, breast carcinoma, cardiac pathology, and liver disease should not be prescribed androgens and if so, cautious management is necessary. Monitoring of liver function tests and lipid profiles periodically is advisable.[59]

Besides these, various sorts of psychotherapies like relationship intervention and sex therapy may be advised. Proper management of depression in menopausal women is beneficial. Transdermal and oral preparation is also suggested based on the patient's profile and tolerability.[44]

Conclusion

Almost every woman in her late forties comes across a few physical and mental ordeals due to the fluctuation of sex steroid hormones. Most of these women are affected by vasomotor symptoms, insomnia, depression, anxiety, and cognitive impairment. The perimenopausal period is the time when these symptoms appear and may last for years. These symptoms may cause disruption in daily life activities and social and occupational functioning.

Hormonal and non-hormonal therapy has been suggested to treat menopause symptoms based on the patient's condition. Non-hormonal therapy includes the prescription of SSRIs and SNRIs. In SSRIs, Paroxetine and Escitalopram have been demonstrated to have better efficacy whereas in SNRIs Venlafaxine and Desvenlafaxine have equal outcomes for the treatment of Vasomotor symptoms. Poor sleep quality has been reported by around 50% of women and this has been attributed to multiple factors such as advancing age, Vasomotor symptoms, mood disorders, etc. Depression

during the perimenopausal transition is another problem that causes significant impairment in interpersonal, occupational, and social settings. Most women entering the menopausal transition may have trouble in remembering names and verbal information. Hormone replacement therapy if administered right before the onset of menopause may have a better outcome in cognitive functions. Dementia is more common in women and the role of Estrogen hormone has been demonstrated in various studies regarding this though a large, randomized placebo-controlled study (WHIMS) showed that Menopausal Hormone Therapy (MHT) could not produce the desired results in terms of cognitive function improvement. Acetylcholine esterase inhibitors like Donepezil have some benefit in slowing the progress but a complete cure has not been demonstrated. Atomoxetine has been shown to improve cognitive functions. Vortioxetine is another SSRI commonly used in depression, which has shown some benefits in improving hot flashes and cognitive symptoms. Sexual dysfunction is another domain of symptoms that are being faced by menopausal females. DHEA and vaginal Estradiol may be helpful in dyspareunia. Various studies suggest the use of testosterone may improve impairment in desire and frequency. Androgens if administered, should be monitored cautiously.

Overall, lifestyle modification such as regular physical and mental exercise, the use of green and leafy vegetables, milk, and fish in the diet, regular check-up, and appropriate management is necessary for menopause and its related symptoms.

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