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A REVIEW ON POST MENOPAUSAL SYNDROME: AN ACT OF AWARENESS

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Abstract

Menopause is one of the most significant events in a woman's life and brings in a number of physiological changes that affect the life of a woman permanently. There have been a lot of speculations about the symptoms that appear before, during and after the onset of menopause. These symptoms constitute the postmenopausal syndrome; they are impairing to a great extent to the woman and management of these symptoms has become an important field of research lately. With improvements in average life expectancy, women live an increased proportion of their lives in the Postmenopause. The consequences of oestrogen loss are the early symptoms (psychological and vasomotor), the genitourinary syndrome (intermediate), as well as postmenopausal osteoporosis with increased risk of fractures and cardiovascular diseases (late). Menopausal hormone therapy is indicated for relief of the acute symptoms of menopause and for treatment of urogenital atrophy. It should be administered in the lowest effective dose for the shortest period of time.

Keywords: Menopause, vasomotor, cognitive, hormone therapy

INTRODUCTION [1, 2]

The period of women's ageing that signifies the change from the reproductive to the non- reproductive stages of life is known as the menopausal transition (premenopause). It lasts for four to seven years. According to the Stages of Reproductive Ageing Workshop (STRAW), it may be separated into an early and late phase and typically lasts from the age of 47 till menopause. Menstrual cycles are regular during the early stages of menopause, however they are not the typical duration. A shortened follicular phase typically results in shorter menstrual periods. Because inhibin has no negative feedback effect, FSH

levels rise as inhibin levels fall. Oestradiol levels may potentially momentarily rise as a result. Two or more missed menstrual cycles and an increased frequency of anovulatory periods are characteristics of the late menopausal transition. A relative excess of oestrogen and a lack of progesterone's stabilising action result, which may cause dysfunctional uterine haemorrhage. The menopause is the last menstrual cycle that lasts for a year without a subsequent one. The phase between irregular menstrual cycles and a year following menopause is known as the perimenopause (climacteric). The stage of a woman's life after menopause is known as the postmenopause. It is distinguished by a high level of FSH (>40 IU/l) and low serum oestradiol (<20 pg ml—1 or 73 pmol l—1).

The typical age for menopause start is between 49 and 51 years old, and this hasn't changed in recent decades. Women now spend a larger percentage of their lives in the postmenopausal phase due to increases in average life expectancy. Understanding the physiological changes associated with the menopausal transition and being aware of available treatments are therefore crucial. Menopause can be caused by iatrogenic causes, such as chemotherapy, pelvic irradiation, or surgical procedures like bilateral oophorectomy, in addition to physiological processes (natural menopause). The onset of primary (hypergonadotropic) hypogonadism before to the age of 40 is known as primary ovarian insufficiency, or premature ovarian failure.

Climacteric (menopausal) syndrome [3]

Climacteric syndrome, or loss, can impact the entire body. Premenopausal women already exhibit the early signs of oestrogen insufficiency. Usually, they go away on their own in two to five years. Acute symptoms might have a vegetative (vasomotor) or psychological cause. Irritability, mood swings, exhaustion, restless nights, anxiety, sadness, forgetfulness, loss of focus, and diminished libido are examples of psychological symptoms. Vasomotor symptoms, which include headache, palpitations, hot flashes, and night sweats, are the most common climacteric symptoms. Usually, the face, neck, and chest have hot flushes. They last between one and five minutes. Peripheral vasodilation causes a brief rise in skin temperature and a fall in core temperature. One of the main causes of hot flashes is a sharp drop in oestrogen levels, called oestrogen withdrawal.

The effects of oestrogen are because practically every organ has oestrogen receptors. Hot flushes are not linked to a persistently low oestrogen level, as in women with Turner's syndrome. It has been proposed that the hypothalamus thermoregulatory set point becomes unstable during the menopausal transition, resulting in a decreased threshold. Even little variations in the core body temperature can trigger the activation of heat dissipation systems. Lowering the thermoregulatory set point has been linked to neurotransmitters like serotonin and norepinephrine. Furthermore, it has been proposed that the pathophysiology of hot flashes may include compromised sympathetic nervous system regulation of cutaneous blood flow.

A few months to a few years following menopause, intermediate signs of oestrogen depletion manifest. Vaginal dryness, dyspareunia, pruritus vulvae, recurrent UTIs, and urine incontinence (genitourinary syndrome of menopause) are all symptoms of urogenital atrophy. Uterine prolapse, cystocele, and rectocele can all be exacerbated by urogenital atrophy. Joint discomfort, wrinkles, and skin atrophy are other signs of connective tissue (collagen) loss. Postmenopausal osteoporosis, which increases the

risk of fractures and cardiovascular illnesses, is a late consequence of oestrogen depletion. Trabecular bone loss is a hallmark of postmenopausal osteoporosis. Women who are of reproductive age are thought to be immune to cardiovascular diseases. However, following menopause, women's cardiovascular morbidity and death are rapidly rising.

The protective actions of oestrogens explain this. They promote vasodilation, improve insulin sensitivity, and have a positive impact on the lipid profile. Conversely, oestrogens cause the liver to produce clotting factors. According to the Heart and Estrogen/Progestin Replacement Study, the latter may be the reason why menopausal hormone treatment is detrimental during the first year of usage and does not help postmenopausal women prevent coronary heart disease subsequent to menopause. Furthermore, prospective, randomised clinical evidence shown that menopausal hormone treatment raises the risk of stroke and coronary heart disease in healthy postmenopausal women over the age of 70 (Women's Health Initiative study).

VASOMOTOR SYMPTOMS [4-5]

Up to 75% of women in their perimenopausal years experience vasomotor symptoms. Most women experience symptoms for one to two years following menopause, although some may experience them for ten years or more. The main reason women seek treatment throughout menopause is because of hot flashes. In addition to interfering with everyday tasks and disturbing women at work, hot flashes often cause sleep disturbances. During the menopausal transition, many women feel emotional instability and trouble focussing. If these cognitive and emotional problems are a result of sleep disturbance and the ensuing daytime weariness, treating vasomotor symptoms might help. Thyroid function tests should be carried out if vasomotor symptoms are unusual or unresponsive to treatment since the prevalence of thyroid illness rises with age in women.

It is still unclear what physiological processes underlie heat flashes. An elevated core body temperature, metabolic rate, and skin temperature are caused by a central event that is most likely started in the hypothalamus; in some women, this reaction causes peripheral vasodilation and perspiration. Dopaminergic, serotoninergic, or noradrenergic stimulation can all cause the main event. Despite the fact that an LH surge frequently coincides with a hot flush, it is not the reason since women who have had pituitary gland removals also experience vasomotor symptoms. It's unclear exactly how oestrogen affects these processes. Oestrogen withdrawal, not just a lack of it, is the cause of vasomotor symptoms.

Treatment [6-13]

The best treatment for vasomotor symptoms and the resulting sleep disruption is systemic oestrogen therapy. Oral contraceptives may be helpful for healthy perimenopausal women who are still menstruation but are having uncomfortable hot flashes. For many women, hot flashes can also be successfully treated with very-low-dose oestrogen treatment. Endometrial stimulation and minimal adverse effects are common features of low-dose oral esterified and conjugated oestrogens (0.3 mg daily) or transdermal oestradiol (0.025 mg weekly). If a woman has not undergone a hysterectomy, progestin therapy must be administered simultaneously; however, intermittent progestin treatment may be possible with low-dose oestrogen therapy.

Other solutions are available in cases when oestrogen is contraindicated. Some women may choose to use just progestin treatment. Vasomotor symptoms can be successfully treated with megestrol acetate (20 mg twice a day) and medroxyprogesterone acetate (MPA) (20 mg daily). A number of medications that modify central neurotransmitter pathways also work well. Clonidine and other substances that lower central noradrenergic tone alleviate heat flashes. Randomised, placebo-controlled studies have demonstrated a substantial reduction in vasomotor symptoms with clonidine. It can be applied as a weekly transdermal patch (0.1 mg/day) or taken orally (0.1–0.2 mg/day). Orthostatic hypotension and sleepiness are possible adverse effects.

Hot flashes can also be effectively relieved by selective serotonin reuptake inhibitors (SSRIs). Menopausal women who suffered from hot flashes found that paroxetine controlled release (12.5 and 25 mg/day) significantly decreased the frequency and intensity of their episodes in a double- blind, randomised, placebo-controlled study. The paroxetine group saw a 62% drop in hot flush composite scores, whereas the placebo group experienced a 38% decrease. When paroxetine was used instead of a placebo, the real hot flush frequency dropped by 3.3 hot flushes per day. No discernible shift in mood or anxiety symptoms was associated with the improvement in vasomotor symptoms. Although the lesser dosage was more tolerated, both levels were effective. Headache, nausea, and sleeplessness were the most frequent adverse effects. A randomised, double-blind, placebo-controlled, crossover study with fluoxetine (20 mg/day) also showed a little reduction in symptoms. Not every study found that SSRIs improved vasomotor symptoms. Neither citalopram (10–30 mg/day) nor fluoxetine significantly reduced hot flashes in a 9-month,double-blind, parallel-group experiment when compared to a placebo.

Although there is a higher chance of side effects, altering other core neurotransmitters with other antidepressants may also be beneficial. In a controlled experiment, venlafaxine (75 mg/day)dramatically decreased hot flashes. Compared to 27% in the placebo group, hot flush ratingsdropped 61% in the venlafaxine group. Anorexia, nausea, and dry mouth were among theadverse effects that were considerably more common in the group receiving aggressive therapy. Despite being frequently advised, a placebo-controlled, randomised, crossover study found thatvitamin E (800 IU/day) very slightly decreased hot flashes. Compared to women of averageweight and nonsmokers, overweight women and smokers experience more severe vasomotorsymptoms. These results offer further justifications for women to quit smoking and reduce their body weight.

UROGENITAL ATROPHY [14]

Urogenital atrophy causes vaginal dryness and pruritus, dyspareunia, dysuria, and urinary urgency, all of which are common issues in menopausal women that respond well to treatment. Systemic oestrogen therapy is an effective way to relieve these symptoms, as it has minimal endometrial stimulation. Low-dose oestrogen cream (0.5 g) is effective when used only once to three times per week, and an oestradiol vaginal tablet (25 g) inserted twice a week may be easier to use and less messy than oestrogen cream. Women who use vaginal oestrogen therapy should be asked to report any vaginal bleeding, and any bleeding should be thoroughly assessed. Usually, women who use low-dose vaginal oestrogen are not prescribed systemic progestin therapy.

When there is urogenital atrophy, lubricants are a non-hormonal option for easing sexual pain. In postmenopausal women, vaginal oestrogen treatment has been demonstrated to lower the risk of recurrent urinary tract infections and to lessen urine symptoms including frequency and urgency. It's uncertain how oestrogen treatment affects urine incontinence. Some research' findings indicate that oestrogen medication can alleviate incontinence, while other studies' findings indicate that the condition becomes worse.

OSTEOPOROSIS [15-18]

Osteoporosis frequently causes musculoskeletal symptoms, such as back pain, fractures from minor trauma, reduced height, and limited mobility. When choosing a course of therapy, it's critical to assess a woman's osteoporosis risk factors and take into account bone mineral density test for high-risk women. Age, Asian or Caucasian race, family history, short stature, history of fractures, early menopause, and previous oophorectomy are risk factors that cannot be changed. Reduced calcium and vitamin D consumption, smoking, and a sedentary lifestyle are all modifiable risk factors. Anovulation during the reproductive years (due to excessive exercise or an eating problem, for example), hyperthyroidism, hyperparathyroidism, chronic renal disease, and illnesses requiring systemic corticosteroid usage are among the medical disorders linked to an elevated risk of osteoporosis.

DEPRESSION [19-21]

An estimated 20% of women experience depression at some time throughout menopause, despite the fact that the majority go through the transition without any mental health issues. Research on mood during menopause has typically shown that the risk of depression is higher during the perimenopause and lowers over the postmenopausal years. According to a cohort research called the Penn Ovarian Ageing research, depression symptoms rose throughout the menopausal transition and then fell following menopause. A past history of depression and changes in reproductive hormone levels linked to low mood were the best indicators of depressed mood.

Pathophysiology

Changing and decreasing oestrogen levels are probably a contributing factor in perimenopausal depression. There are several ways that steroid hormones, including oestrogen, affect the central nervous system (CNS). They affect membrane permeability, for example, and promote the production of neurotransmitters and receptor expression. Serotonin and norepinephrine are believed to be the neurotransmitters most closely linked to the physiological aetiology of depression, and oestrogen amplifies their effects. Oestrogen, among other things, inhibits the breakdown of serotonin and norepinephrine by lowering monoamine oxidase (MAO) activity in the central nervous system. Furthermore, oestrogen downregulates 5-HT2 receptors, upregulates 5-hydroxytryptamine (5-HT1) receptors, and enhances serotonin production. Additionally, oestrogen raises norepinephrine activity in the brain, perhaps via inhibiting the enzymes catechol-O-methyltransferase and MAO, which reduces reuptake and breakdown.

Life stressors

The higher prevalence of depression among women may be attributed to societal norms and expectations. Perimenopausal depression appears to be more common in women who experience certain kinds of stress. Among these stresses are the following:

- Insufficient social support;
- Joblessness;
- Menopause surgery;
- Poor general health.

Women with relatively low educational status are more likely to have dysphoric moods during the early perimenopausal transition. Consequently, low educational attainment might be a sign of other stresses, including persistently low socioeconomic position.

Psychological or social conditions

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To explain why women may experience depression during the perimenopause, a variety of social and psychological hypotheses have been proposed. The following elements are connected to a few of these:

- Modification in the function of childbearing;
- Fertility loss, which might be linked to the loss of a fundamental purpose in life;
- Empty nest syndrome
- The importance placed on youth by society (women report less symptoms during themenopausal transition in communities that value age).

Treatment

Standard antidepressants are the first-line therapy for serious depression. The most popular medications for treating perimenopausal depression are SSRIs. SSRIs are usually regarded as safe and beneficial. Action starts four to six weeks later. In addition to a number of frequent side effects including headache, jitteriness, dizziness, sedation or activation, sleeplessness, akathisia, and gastrointestinal side effects like nausea, diarrhoea, and anorexia, they also carry the risk of serotonin syndrome.

COGNITIVE FUNCTIONS [22-23]

Women who are perimenopausal or recently postmenopausal frequently complain of memory issues. Given the higher prevalence of cognitive symptoms in menopausal women, it is likely that memory issues in this demographic are more closely linked to the menopause transition than to ageing. The causal

significance of oestrogen in the cognitive impairments experienced by perimenopausal and recent postmenopausal women is supported by clinical trials that describe the improvement of cognition with HRT. It is unclear how the menopausal transition may affect some cognitive areas, such as verbal memory, attention, and learning ability.

The apparent correlation between certain women's cognitive challenges and the menopausal transition raises the possibility that these cognitive disruptions are linked to the hormonal changes associated with menopause. The consequences of the shifting hormonal environment in the parts of the brain that affect cognition or sleep disturbance brought on by nocturnal hot flashes may cause cognitive problems.

SEXUAL DYSFUNCTION [24-27]

The precise prevalence and aetiology of sexual dysfunction during menopause are unknown, although many women experience it. Reduced arousal or the capacity to experience an orgasm during sexual interactions, as well as a diminished interest or desire to begin activity, are all examples of sexual dysfunction. Sexual dysfunction frequently has a complex aetiology, involving psychological issues like depression or anxiety disorders, relationship conflict, problems related to past physical or sexual abuse, medication use, or physical conditions like endometriosis or atrophic vaginitis that make sexual activity uncomfortable. After menopause, female sexual dysfunction is a complicated issue with several causes. To maximise therapy, a thorough assessment of lifestyle, relational, psychological, and physiological factors is necessary. Sexual function may be enhanced by relationship counselling, antidepressant drug adjustments, and treatment for anxiety and sadness. Many women and couples with sexual dysfunction benefit from certain exercises and activities, which are frequently carried out under the supervision of a sex therapist. When genitourinary atrophy is specifically treated with vaginal lubricants or systemic or local vaginal oestrogen therapy, dyspareunia is successfully reduced, and sexual desire and responsiveness may be enhanced. In a major randomised, double-blind, placebo-controlled investigation of women with sexual dysfunction, sildenafil citrate did not work. For women going through menopause who have low testosterone levels and no other known reason for their sexual dysfunction, androgen therapy may be helpful.

PROBLEMS WITH SLEEP [28-31]

During the menopausal transition, 40–50% of women have insomnia, and mood disorders may or may not be linked to sleep issues. Anxiety, tension, stress, and depressed symptoms are among the issues that women with insomnia are more likely to report than other women. Because exogenous oestrogen has been demonstrated to enhance both subjective and objective sleep by reducing hot flashes, sleep difficulties during menopause have been linked to oestrogen insufficiency. According to a recent study, excessive levels of LH in the late stages of menopause cause poor sleep quality by raising core body temperatures through a thermoregulatory mechanism. It's unclear if the sleep issues are connected to hormone changes, age-related changes in sleep architecture, or other menopausal symptoms (such vasomotor symptoms).

COURSE OF SOME IMPORTANT PSYCHIATRIC DISORDERS DURING MENOPAUSE [32-35]

Schizophrenia [33]

Schizophrenia often initially appears in young adulthood, and beyond early adulthood, the number of new cases in both males and females decreases. Women between the ages of 45 and 50 have a second peak in the incidence of schizophrenia, but men do not exhibit this second peak.

During the menopausal transition, some researchers have seen women with schizophrenia experience a worsening of their condition. These findings could imply that oestrogen modulates the pathogenesis of schizophrenia.

Bipolar disorder [32, 35]

Women with pre-existing bipolar illness have been seen to experience an increase in mood symptoms throughout menopause. According to research, depression episodes during the menopausal transition are more common in women with bipolar illness. Compared to premenopausal years, this demographic seems to experience depressive episodes more frequently. An increase in fast cycling during the menopausal transition was predicted by earlier research, however this finding has not been replicated.

Panic disorder [34]

Perimenopause is a prevalent time for panic anxiety. Menopause may bring on the beginning of a new panic disorder or exacerbate an existing one. Women who have several physical menopausal symptoms may be more susceptible to panic disorder.

Panic episodes were most common among women going through the menopausal transition, according to a cross-sectional study of 3369 postmenopausal women between the ages of 50 and
79. Medical comorbidity, functional disability, and adverse life events were linked to panic episodes.

Disorder of obsessive-compulsive behaviour [36-37]

Menopause may bring on a recurrence of obsessive-compulsive disorder (OCD), a shift in OCD symptoms, or the development of OCD. Pregnancy and the menstrual cycle have been linked to OCD fluctuations, indicating that hormone levels may play a role in the illness.

Diagnosis

Typical clinical signs are used to diagnose climacteric syndrome. Although they may be determined, FSH and oestradiol levels are not necessary for menopause diagnosis. A complete medical history is required to determine the risk factors for venous thromboembolism, osteoporosis, and cardiovascular diseases. General laboratory tests, including complete blood count, ions, glucose, liver and renal function, lipid profile, coagulogram, and urine analysis, should be performed in addition to gynaecological physical examinations (bimanual, colposcopy, cervical cytology, and breast exam). It is also necessary to do mammography and transvaginal ultrasonography with endometrial thickness assessment. To assess bone mineral density on the lumbar spine and femoral neck, osteodensitometry using DEXA (Dual-Energy X-Ray Absorptiometry) is also advised. Involvement of other medical professionals (family physician,

rheumatologist, cardiologist, diabetologist, urologist, psychiatrist, psychologist) may also be needed.

Management of Menopausal hormone therapy [38-39]

Women who are perimenopausal should be aware of the physiological changes that occur throughout the menopausal transition. They ought to be urged to lead healthy lives, abstain from smoking, limit alcohol intake, maintain a balanced diet, and engage in regular exercise. After a patient's benefit/risk profile has been evaluated and their written informed permission has been obtained, menopausal hormone treatment should be administered. An expert in obstetrics and gynaecology should prescribe it.

Menopausal hormone therapy is recommended to treat urogenital atrophy and alleviate the acute vasomotor and psychological symptoms of menopause. For the shortest amount of time, the lowest effective dosage should be given. To reduce the hazards, the medication should be started before the age of 60 or within ten years following menopause. Every year, each benefit/risk profile needs to be reevaluated. It is not advised to continue treatment for more than five years.

Bisphosphonates, which are agents specific to bones, are more suited for treating and preventing osteoporosis over the long term.

Breast cancer, endometrial cancer, venous thromboembolic illness, coronary artery disease, stroke, acute liver disease, intermittent porphyria acuta, unexplained abnormal vaginal bleeding, and pregnancy are all absolute contraindications to menopausal hormone treatment.

Menopausal hormone treatment delivery methods and schedules

Oral, transdermal (patch, gel, spray), intravaginal (tablet, cream, suppository), intrauterine (Mirena®), nasal, subcutaneous (implant), and intramuscular (injection) are the various ways that menopausal hormone treatment can be administered. Oral therapy options include tibolone and natural oestrogens (17b-oestradiol, conjugated oestrogens, oestriol, and oestradiol-valerate). Menopausal hormone treatment does not use ethinyl oestradiol, the synthetic oestrogen included in oral contraceptives.

Women who have risk factors for venous thromboembolism, liver illness, or gastrointestinal issues are better suited for transdermal medication as it eliminates the first-pass hepatic impact. Urogenital atrophy can be effectively treated with intravaginal therapy, which also has hepatoprotective properties. If systemic hormone treatment is contraindicated, it may also be used.

Only oestrogen is required for women who have had a previous hysterectomy. In order to avoid endometrial hyperplasia and cancer, women with an intact uterus must additionally take progestogen for endometrial protection. Regular withdrawal bleeding occurs during the perimenopause when progestogen is added to successive preparations for 10–14 days per month. Women who are at least a year past their last menstrual cycle are treated with continuous combined hormone treatment, which involves administering the same dosage of progestogen and oestrogen every day. These preparations cause amenorrhoea and endometrial shrinkage. In the initial months of usage, however, sporadic bleeding and spotting are typical.

CONCLUSION

Women spend a larger percentage of their lives in the postmenopausal stage as average life expectancy rises. Women who are perimenopausal should be aware of the physiological changes that occur throughout the menopausal transition. They ought to be motivated to lead healthy lives. Individual

benefit/risk profiles should be evaluated before beginning menopausal hormone treatment. For the shortest amount of time, the lowest effective dosage should be given. To reduce the hazards, the medication should be started before the age of 60 or within ten years following menopause. Each year, the benefit/risk profile must be reevaluated on an individual basis.

References

1. Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W, Woods N. Executive summary: stages of reproductive aging Workshop (STRAW). Fertil Steril 2001;76:874–8. https://doi.org/ 10.1016/s0015-0282(01)02909-0.
2. Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop: addressing the unfinished agenda of staging reproductive aging. Climacteric 2012;15:105–14.https://doi.org/10.3109/13697137.2011.650656.
3. Rapkin AJ. Vasomotor symptoms in menopause: physiologic condition and central nervous system approaches to treatment. Am J Obstet Gynecol 2007;196:97–106. https://doi.org/10.1016/j.ajog. 2006.05.056.
4. Bachmann GA. Menopausal vasomotor symptoms: a review of causes, effects and evidence- based treatment options. J Reprod Med 2005;50:155–65.
5. Utian WH, Shoupe D, Bachmann G, Pinkerton JV, Pickar JH. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. Fertil Steril 2001;75:1065-79.
6. Genant HK, Lucas J, Weiss S, Akin M, Emkey R, McNaney-Flint H, et al. Low-dose esterified estrogen therapy: Effects on bone, plasma estradiol concentrations, endometrium, and lipid levels. Estratab/Osteoporosis Study Group. Arch Intern Med 1997;157:2609-15.
7. Weiss SR, Ellman H, Dolker M. A randomized controlled trial of four doses of transdermal estradiol for preventing postmenopausal bone loss. Transdermal Estradiol Investigator Group. Obstet Gynecol 1999;94:330-6.
8. Schiff I, Tulchinsky D, Cramer D, Ryan KJ. Oral medroxyprogesterone in the treatment of postmenopausal symptoms. JAMA 1980;244:1443-5.
9. Freedman RR, Woodward S, Sabharwal SC. Alpha 2-adrenergic mechanism in menopausal hot flushes. Obstet Gynecol 1990;76:573-8.
10. Nagamani M, Kelver ME, Smith ER. Treatment of menopausal hot flashes with transdermal administration of clonidine. Am J Obstet Gynecol 1987;156:561-5.
11. Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: A randomized controlled trial. JAMA 2003;289:2827-34.
12. Loprinzi CL, Sloan JA, Perez EA, Quella SK, Stella PJ, Mailliard JA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. J Clin Oncol 2002;20:1578-83.
13. Suvanto-Luukkonen E, Koivunen R, Sundström H, Bloigu R, Karjalainen E, Häivä-Mällinen L, et al. Citalopram and fluoxetine in the treatment of postmenopausal symptoms: A prospective, randomized, 9-month, placebo-controlled, double-blind study. Menopause 2005;12:18-26.
14. Eriksen B. A randomized, open, parallel-group study on the preventive effect of anestradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. Am J Obstet Gynecol 1999;180:1072-9.
15. Grady D, Brown JS, Vittinghoff E, Applegate W, Varner E, Snyder T, et al. Postmenopausal hormones and incontinence: The Heart and Estrogen/Progestin Replacement Study. Obstet Gynecol 2001;97:116-20.

16. Cauley JA, Zmuda JM, Ensrud KE, Bauer DC, Ettinger B, Study of Osteoporotic Fractures Research Group. Timing of estrogen replacement therapy for optimal osteoporosis prevention. J Clin Endocrinol Metab 2001;86:5700-5.

17. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.

18. Prestwood KM, Kenny AM, Kleppinger A, Kulldorff M. Ultralow-dose micronized 17beta-estradiol and bone density and bone metabolism in older women: A randomized controlled trial. JAMA 2003;290:1042-8.

19. Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB, Hollander L. Hormones and menopausal status as predictors of depression in women in transition to menopause. Arch Gen Psychiatry 2004;61:62-70.

20. Maartens LW, Knottnerus JA, Pop VJ. Menopausal transition and increased depressive symptomatology: A community based prospective study. Maturitas 2002;42:195-200.

21. Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: The Harvard study of moods and cycles. Arch Gen Psychiatry 2006;63:385-90.

22. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: The Women's Health Initiative Memory Study: A randomized controlled trial. JAMA 2003;289:2651-62.

23. Espeland MA, Rapp SR, Shumaker SA, Brunner R, Manson JE, Sherwin BB, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. JAMA 2004;291:2959-68.

24. Basson R, McInnes R, Smith MD, Hodgson G, Koppiker N. Efficacy and safety of sildenafil citrate in women with sexual dysfunction associated with female sexual arousal disorder. J Womens Health Gend Based Med 2002;11:367-77.

25. Bachmann G, Bancroft J, Braunstein G, Burger H, Davis S, Dennerstein L, et al. Female androgen insufficiency: The Princeton consensus statement on definition, classification, and assessment. Fertil Steril 2002;77:660-5.

26. Sherwin BB, Gelfand MM. Sex steroids and affect in the surgical menopause: A double-blind, cross-over study. Psychoneuroendocrinology 1985;10:325-35.

27. Lobo RA, Rosen RC, Yang HM, Block B, Van Der Hoop RG. Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. Fertil Steril 2003;79:1341-52.

28. Soares CN, Joffe H, Steiner M. Menopause and mood. Clin Obstet Gynecol 2004;47:576-91.

29. Murphy PJ, Campbell SS. Sex hormones, sleep, and core body temperature in older postmenopausal women. Sleep 2007;30:1788-94.

30. Krystal AD. Depression and insomnia in women. Clin Cornerstone 2004;6 Suppl 1B: S19-28.

31. Miller EH. Women and insomnia. Clin Cornerstone 2004;6 Suppl 1B: S8-18.

32. Shin K, Shapiro C. Menopause, sex hormones, and sleep. Bipolar Disord 2003;5:106-9.

33. Häfner H. Gender differences in schizophrenia. Psychoneuroendocrinology 2003;28 Suppl 2:17-54.

34. Marsh WK, Templeton A, Ketter TA, Rasgon NL. Increased frequency of depressive episodes during the menopausal transition in women with bipolar disorder: Preliminary report. J Psychiatr Res 2008;42:247-51.

35. Burt VK, Rasgon N. Special considerations in treating bipolar disorder in women. Bipolar Disord 2004;6:2-13.

36. Smoller JW, Pollack MH, Wassertheil-Smoller S, Barton B, Hendrix SL, Jackson RD, et al. Prevalence and correlates of panic attacks in postmenopausal women: Results from an ancillary study to the Women's Health Initiative. Arch Intern Med 2003;163:2041-50.

37. Lochner C, Hemmings SM, Kinnear CJ, Moolman-Smook JC, Corfield VA, Knowles JA. Corrigendum to gender in obsessive-compulsive disorder: Clinical and genetic findings. Eur Neuropsychopharmacol 2004;14:437-45.

38. Baber RJ, Panay N, Fenton A, IMS Writing Group. IMS recom- mendations on women's midlife health and menopause hormone therapy. Climacteric 2016;19:109–50. https://doi.org/10.3109/ 13697137.2015.1129166.

39. de Villiers TJ, Hall JE, Pinkerton JV, et al. Revised global consensus statement on menopausal hormone therapy. Climacteric 2016;19: 313–5. https://doi.org/10.1080/13697137.2016.1196047