Review Article

Pharmacotherapy of Perimenopausal and Menopausal Symptoms: An Overview

Dr. Virendra Kushwaha*, Dr. Pooja Agrawal, Dr. Harsh Vekaria, Dr. Brijesh Pathak, Dr. Sameer Siddiqui
Department of Pharmacology, GSVM Medical College, Kanpur, UP, India.
***Corresponding author's E-mail:** vkushwaha1970@gmail.com

Received: 05-01-2025; **Revised:** 28-03-2025; **Accepted:** 10-04-2025; **Published online:** 20-04-2025.

ABSTRACT

Perimenopause and menopause are crucial life transitions marked by hormonal changes, leading to symptoms like menstrual irregularities, hot flashes, mood swings, osteoporosis, and cardiovascular risks. Symptom prevalence varies by region and ethnicity, influenced primarily by fluctuations in estrogen, progesterone, FSH, and inhibin. Hormone replacement therapy (HRT) remains the most effective treatment for vasomotor and genitourinary symptoms, with options like estrogen therapy, combined HRT, and tissue-selective estrogen complexes (TSECs). For those unable to take hormones, non-hormonal treatments such as SSRIs, SNRIs, gabapentin, and clonidine provide relief. Emerging therapies like neurokinin receptor antagonists and stellate ganglion block (SGB) show promise in symptom control. A multidisciplinary approach that integrates medical, psychological, and lifestyle strategies can ensure a smoother transition through menopause and improve the quality of life for affected individuals. While pharmacotherapy offers significant benefits, personalized treatment plans considering individual risk factors, evolving health needs, and patient preferences are essential for optimizing long-term outcomes and overall well-being.

Keywords: Perimenopause, Menopause, Lifestyle changes, Hormone replacement therapy.

INTRODUCTION

The term Perimenopause means "around menopause" which refers to the time during which female body makes the natural transition to menopause, marking the cessation of the reproductive years. Perimenopause is also known as menopausal transition. Females go through perimenopause at different ages. Signs of progression toward menopause, such as menstrual irregularity, sometime in 40s. But some women notice changes as early as their mid-30s[1]. Perimenopause, or the menopausal transition, encompasses that period during which physiologic changes mark progression toward a woman's final menstrual period (FMP). This phase begins with the onset of menstrual irregularities and continues until a woman reaches menopause, or one year after amenorrhea has occurred[2].

Menopause is the time in women's lives when menstrual periods stop permanently, and they are no longer able to bear children. Menopause is defined as the permanent cessation of menstruation and ovulation[3-4]. World Menopause Day is celebrated on 18th October every year. Medical professionals often define menopause as when a woman has not had any menstrual bleeding for a year[5]. It may also be defined by a decrease in hormone production by the ovaries[6]. After 12 months of amenorrhea without pathological etiology, menopause is considered "natural" or "spontaneous." Menopause can also be induced by surgical or pharmacological means. It occurs naturally between the ages of 42 and 58 and is a consequence of reproductive senescence [7-9].

EPIDEMIOLOGY

The prevalence of transition of females from the reproductive phase to the menopausal phase is estimated to be about 50 million cases worldwide annually[10]. In 1990 there were 467 million post-menopausal women in the world, by 2030, menopausal women are projected to increase to 1.2 billion worldwide[11].

The prevalence of menopausal symptoms differs in women according to areas and countries where they live, the menopausal symptoms range from 74% of women in Europe, 36-50% in North America, 45-69% in Latin America, and 22-63% in Asia[12]. In India, the transition from reproductive age to menopause typically occurs between 45 and 55 years of age. Approximately 14.66% of women aged 30 to 49 are in menopause, with higher rates in rural areas (15.96%) compared to urban areas (12.19%). The prevalence of menopause does not vary by race. The ethnic differences in the symptoms experienced during the menopausal transition were noted. Asian women had experienced the smallest number of menopausal symptoms compared with all other ethnic groups, but African American women had experienced the largest number of menopausal symptoms compared with other ethnic groups[13].

PERIMENOPAUSE TO MENOPAUSAL TRANSITION

Perimenopause to menopausal transition is a natural and inevitable process that occurs in every woman's life. Studies of the menopausal transition have taught us a great deal about the changes that occur in populations of women from cohorts around the world[14-17]. Perimenopause, or the menopausal transition, begins with menstrual irregularities and continues until menopause (1-year after amenorrhea). It includes early (mostly regular cycles) and late (amenorrhea ≥60 days) transition stages[18]. The stages of reproductive aging have been well described with the acronym STRAW[19-21]. Table. 1 shows phase of perimenopausal to menopausal transition.

CHANGES THAT OCCUR IN THE PERIMENOPAUSAL AND MENOPAUSAL PHASE

1. **COMMON CHANGES IN THE PERIMENOPAUSAL PHASE:** Throughout the perimenopausal to menopausal transition, some subtle and some not-so-subtle changes in the body that may take place during the perimenopausal phase are as follows:

- **Irregular periods**: As ovulation becomes more unpredictable, the length of time between periods may be longer or shorter, flow may be light to heavy and cycles may be skipped[22].
- **Hot flashes and sleep problems**: Hot flashes are common during perimenopause. The intensity, length, and frequency vary. Sleep problems are often due to hot flashes or night sweats, but sometimes sleep becomes unpredictable even without them[23].

Mood changes: Mood swings, irritability, or increased risk of depression may happen during perimenopause. **Vaginal and bladder problems:** When estrogen levels diminish, vaginal tissues may lose lubrication and elasticity, making intercourse painful. Low estrogen may also leave be more vulnerable to urinary or vaginal infections. **Increased risk of osteoporosis,** Urinary urgency[24] and Breast tenderness[25].

Table 1: Perimenopausal to menopausal transition

	-5	-4	-3	-2	-1	+1	+2
Terminology	Reproductive			Menopausal transition		Postmenopause	
	early	peak	late	early	late	early	late
				perimenopause			
Duration of stages	variable			variable		①	② 4 Years / Until demise
Menstrual cycle	Variable to regular		Regular	Variable cycle length (>7 days different from normal)	≥ 2 skipped cycles and an interval of amenorrhea (≥ 60 days)		None
endocrine	Normal FSH		↑FSH	↑FSH		↑FSH	

Final menstrual period (FMP)

COMMON CHANGES IN THE MENOPAUSAL PHASE

- The incidence of cardiovascular disease among menopausal women significantly increases after menopause. Specifically, the risk of coronary heart disease is two to threefold higher for postmenopausal women compared with premenopausal women of the same age[26,27].
- Vaginal dryness, pain, itching, or discomfort during sex, hot flushes, sudden feelings of hot or cold in face, neck, and chest which can make menopausal women feel dizzy[26]. Difficulty sleeping, which may be a result of night sweats makes menopausal women feel tired and irritable during the day[27].
- Memory lapses, brain fog, and poor concentration during menopause are often mistaken for stress. Up to 62% of women experience these due to estrogen decline, sleep issues, and anxiety[27].
- Hair loss: During perimenopause, hair can become thinner and grow slower than previously experienced due to a decline in progesterone and estrogen. A decline in these two hormones triggers male hormones; these hormones can make hair follicles shrink which causes hair loss[28].
- Urinary Tract Infections: During menopause, some women may experience more urinary tract infections. Lowered levels of estrogen and changes in the urinary tract make women more susceptible to infection[29,30].
- Headaches, migraines, muscle aches, joint pains, weight gain, and skin changes including dry and itchy skin[31].

Breast soreness. This may be in both breasts or just one and may feel different from the 'usual' discomfort associated with the period. The soreness can feel sharp or be a throbbing or burning sensation [32]. Figure 1 shows different symptoms of Perimenopausal and menopausal phase

HORMONAL CHANGES IN MENOPAUSAL TRANSITION

- **FSH:** FSH, produced by the pituitary gland, fluctuates during menopause, affecting estrogen levels. Postmenopausal FSH is 10–15 times higher, while LH rises 3–5 times. Inhibin decline may directly indicate reduced ovarian reserve[33-36].
- **Inhibin:** Inhibins are glycoprotein hormones made up of disulfide-linked subunits linked to either a βA-subunit (inhibin A) or a βB-subunit (inhibin B), and secreted under the influence of FSH and LH. One of the first hormonal changes is a decrease in a hormone called inhibin [37-39]. The ovary makes inhibin and it tells the

pituitary gland to make less follicle-stimulating hormone (FSH)[40]. As inhibin levels go down, FSH levels go up. The changes in blood levels of these hormones can be found months to years before a woman begins the transition to menopause[41,42].

- **Progesterone:** Progesterone is an endogenous steroid hormone that is commonly produced by the adrenal cortex as well as the gonads, which consist of the ovaries and the testes. Progesterone is also secreted by the ovarian corpus luteum during the first ten weeks of pregnancy, followed by the placenta in the later phase of pregnancy[43]. As a woman ovulates less often, progesterone levels may remain low, causing a missed menstrual period.
- **AMH** - Antimüllerian hormone (AMH), like inhibin, is made by the ovaries. As a woman ages, her AMH levels drop and are not detectable a few years before a female enters menopause[44].
- It is important to understand that hormonal changes vary from woman to woman. While high FSH and low AMH and inhibin levels are often seen in the menopause transition, there is no one specific blood test that can predict or diagnose that a woman is in the menopause transition.

PHARMACOTHERAPY AND LIFESTYLE CHANGES

Pharmacotherapy for perimenopausal and menopausal symptoms typically focuses on relieving specific symptoms such as hot flashes, mood changes, and vaginal dryness. It is important to note that not all females will require pharmacological treatment, as many can manage their symptoms with lifestyle changes and non-pharmacological interventions.

LIFESTYLE CHANGES: Lifestyle changes play a significant role in managing the physical and emotional symptoms of menopause. These changes can help improve overall well-being, alleviate specific symptoms, and promote better health during this life transition. Here are some lifestyle changes that can be beneficial during menopause:

- **Healthy diet**[45]**:** Maintain a balanced diet rich in fruits, vegetables, whole grains, lean proteins, and low-fat dairy products. Increase calcium and vitamin D intake to support bone health. Limit caffeine and alcohol, as they can exacerbate hot flashes and sleep disturbances.
- **Regular Exercise**[46]**:** Engage in regular physical activity, including cardiovascular exercises (e.g., walking, jogging, swimming), strength training, and flexibility exercises. Exercise can help manage weight, improve mood, reduce hot flashes, and promote heart and bone health.
- **Weight Management**[47]**:** Maintaining a healthy weight can help reduce the risk of various health issues, including heart disease and joint problems. Hormonal changes during menopause can sometimes lead to weight gain, so monitoring calorie intake and staying active is crucial.
- **Stress Reduction**[48]**:** Practice stress-reduction techniques such as mindfulness, yoga, meditation, deep breathing exercises, or progressive muscle relaxation to manage stress and anxiety.
- **Adequate Sleep**[49]**:** Prioritize good sleep hygiene to improve the quality and duration of sleep. Create a comfortable sleep environment and establish a regular sleep schedule. Staying active by playing sports or exercising may help with staying asleep during the night, improve sleep quality and insomnia, and make sleep deeper.
- **Hydration**[50]**:** Stay well-hydrated by drinking plenty of water throughout the day. Reducing caffeine intake, especially in the afternoon and evening, can help with sleep.
- **Smoking Cessation**[51]**:** Smoking is associated with an increased risk of osteoporosis, heart disease, and other health issues that can be exacerbated during menopause, hence smoking cessation can help prevent these mentioned medical conditions.
- **Alcohol Moderation**[52]**:** Limit alcohol consumption, as it can worsen hot flashes and increase the risk of breast cancer.
- **Vaginal Health**[53]**:** For vaginal dryness and discomfort, consider using water-based lubricants or moisturizers to ease discomfort during sexual activity.
- **Regular Health Screenings**[54]**:** Continue to attend routine check-ups with healthcare provider for preventive health screenings and discussions about menopausal symptoms.
- **Social Support**[55]**:** Maintain strong social connections with friends and family for emotional support during this transition.

Remember that every woman's experience of menopause is unique, and what works for one may not work for another. Therefore, a healthcare provider must plan a personalized plan tailored to specific needs and concerns. Lifestyle changes, combined with medical treatments or interventions, can help navigate the challenges of menopause and maintain good health and well-being.

PHARMACOTHERAPY

Pharmacotherapy, or the use of medications, is one approach to managing perimenopausal symptoms. The choice of therapy depends on the specific symptoms, their severity, and the individual's medical history. Below are some of the common pharmacotherapies used to address these symptoms:

1. **Hormone Replacement Therapy (HRT**): Hormone replacement therapy is one of the most effective ways to manage perimenopausal and menopausal

symptoms, particularly those related to hormonal fluctuations. It primarily involves the use of two types of hormones: estrogen and progestin[56].

a. **Estrogen Therapy**: - Estrogen represents the most effective treatment for menopausal vasomotor symptoms and related issues including impaired sleep, irritability, and decreased quality of life. Except for the 0.14 mg ultra-low-dose estradiol patch, all systemic estrogen formulations are approved for the treatment of vasomotor symptoms. Various studies have shown that when adequate progestogen is combined with estrogen, the risk of endometrial neoplasia is not higher than in untreated women. Estrogen can be administered in various forms, including oral pills, transdermal patches, topical creams, and vaginal rings. These treatments help alleviate symptoms like hot flashes, vaginal dryness, and mood swings. They work by replenishing the declining levels of estrogen in the body, thus addressing the underlying hormonal imbalances[56-58]. Table. 2 shows different Estrogen therapy.

b. **Combined HRT**: - For women who have not undergone hysterectomy, a combination of estrogen and progestin is often prescribed. Combined HRT can effectively relieve menopausal symptoms while protecting the uterine lining. There are mainly 2 types of Combined HRT, which can be administered. They are as below:

c. **Sequential Combined Hormone Replacement Therapy (HRT):** Sequential combined HRT involves estrogen followed by progestin to relieve perimenopausal symptoms, regulate cycles, and prevent endometrial hyperplasia. Its use should be individualized, considering risks and benefits, with regular monitoring by a healthcare provider[59-63].

d. **Continuous Combined Hormone Replacement Therapy (HRT):** Continuous combined HRT provides estrogen and progestin to relieve menopausal symptoms and reduce endometrial hyperplasia risk. Treatment should be personalized, considering risks and benefits, with regular monitoring by a healthcare provider for safety and effectiveness[64-69]. Table 4 shows the continuous combined HRT Regimen.

Table 2: Estrogen Therapy

Estrogen Type	Dose	Duration	Method
Estradiol (Oral)	0.5-2 mg daily	Continuous or Cyclic	- Starting dose often low, then adjusted based on response - Cyclic dosing: 21 days on, 7 days off for menstruation
Estradiol (Transdermal Patch)	0.025-0.1 mg/24 hours	Continuous or Cyclic	Patch changed 1-2 times per week
Estradiol (Topical Gel/Cream)	1.25-2.5 mg daily	Continuous or Cyclic	Applied to skin, usually on arms or legs
Estradiol (Vaginal Cream/Tablet/Ring)	0.01-0.1 mg daily	Continuous or Intermittent	- Used for local vaginal symptoms, lower systemic absorption - Often used continuously, but can be cyclic
Conjugated Estrogens (Oral)	0.3-1.25 mg daily	Continuous or Cyclic	Similar dosing to estradiol
Estropipate (Oral)	0.625-2.5 mg daily	Continuous or Cyclic	Similar to conjugated estrogens
Estriol (Vaginal Cream)	0.5-2 mg daily	Continuous	Used for local vaginal symptoms, lower systemic absorption
Ethinyl Estradiol (Oral)	10-50 mcg daily	Continuous or Cyclic	Commonly used in combined oral contraceptives

Table 3: Sequential Combined HRT Regimen[59-63]

Day	Medication	Dose	Route	Administration
1-14	Estrogen (Conjugated Estrogens or Estradiol)	0.625-2 mg/day	Oral or Transdermal	Daily
15-25	Estrogen + Progestogen	Estrogen: 0.625-2 mg/day Progestogen: 5-10 mg/day (Medroxyprogesterone Acetate) or 200-300 mg/day (Micronized Progesterone)	Oral	Daily
26-28/30	No Medication	-	-	Stop both medications

Table 4: Example Continuous Combined HRT Regimen[64-69]

Day	Medication	Dose	Route	Administration
1-28	Estrogen + Progestogen Combination	Estrogen: 0.625-2 mg/day Progestogen: 2.5-5 mg/day (Medroxyprogesterone Acetate) or 100-200 mg/day (Micronized Progesterone)	Oral	Daily

e. Stellate Ganglion Block Method

Stellate Ganglion Block (SGB) may help reduce hot flashes by blocking sympathetic nerve activity. While studies suggest its potential benefits, more research is needed to confirm its effectiveness and long-term safety in menopausal women[70-72].

SGB may improve sleep by reducing pain and stress, which can affect menopausal women. It may also enhance mood and emotional well-being by modulating the sympathetic nervous system, potentially alleviating anxiety and PTSD symptoms [73-75]. SGB for menopause uses lidocaine for quick relief, bupivacaine for longer effects, and sometimes corticosteroids or epinephrine for enhanced benefits[76].

A small RCT on 40 postmenopausal women found stellate ganglion block significantly reduced moderate to severe hot flashes compared to placebo. While overall vasomotor symptoms were similar between groups, active treatment led to greater improvement in symptom frequency and severity.[77] As research in this area continues to evolve, SGB may emerge as a promising option for menopausal symptom management.

2. **ANTIDEPRESSANTS AND MOOD STABILIZERS:** Perimenopause can bring about mood disturbances, such as irritability, anxiety, and depression[79]. Antidepressants and mood stabilizers can help manage these emotional fluctuations[80].

   a. **Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)**: - Medications in these classes, such as fluoxetine, sertraline, and venlafaxine, may be prescribed to stabilize mood and alleviate symptoms of anxiety and depression[81].

   b. **Mood Stabilizers**: - In some cases, mood-stabilizing medications like lithium or valproic acid may be considered to help manage mood swings and irritability[82]

3. **NON-HORMONAL OPTIONS**: For women who cannot or prefer not to use hormone therapy, non-hormonal options are available to manage perimenopausal symptoms[83].

   a. **Gabapentin and Pregabalin**: These anticonvulsant medications are found to be effective in reducing the frequency and severity of hot flashes in some women. - They work by affecting the central nervous system, which can help regulate temperature control[84].

   b. **Clonidine**: This antihypertensive medication may be used to alleviate hot flashes and other vasomotor symptoms. - It affects the brain's regulation of blood vessels and can help reduce the severity of hot flashes[85].

OTHER THERAPY OPTIONS

Local Estrogen Therapy: Local estrogen therapy (creams, tablets, rings) effectively treats vaginal dryness, itching, and pain with minimal systemic risks, directly targeting vaginal tissues for symptom relief[86-88].

Osteoporosis Medications: Declining estrogen during perimenopause accelerates bone loss, increasing osteoporosis risk. Bisphosphonates like alendronate and zoledronic acid improve bone density and reduce fractures[89]. Denosumab, a RANKL-targeting monoclonal antibody, is an alternative. SERMs like raloxifene protect bones while lowering breast cancer risk, ensuring comprehensive bone health management[90]. Calcitonin, though less commonly used, inhibits osteoclasts and provides pain relief in vertebral fractures[91].

BENEFITS OF PHARMACOTHERAPY

1. Relief from Vasomotor Symptoms[92]: Pharmacotherapy effectively reduces vasomotor symptoms like hot flashes and night sweats during menopause. HRT, particularly estrogen, is the most effective treatment. For women unable to use HRT, SSRIs, SNRIs, and gabapentin offer effective non-hormonal alternatives, improving symptom control and quality of life.

2. Mood Stabilization and Mental Health[93-95]: Hormonal fluctuations during menopause contribute to mood disorders like depression and anxiety. HRT, particularly estrogen, stabilizes mood, while SSRIs and SNRIs help manage emotional symptoms. These medications also alleviate vasomotor symptoms, providing dual benefits. A personalized approach ensures effective treatment, enhancing mental health and overall well-being during the menopausal transition.

3. Bone Health and Osteoporosis Prevention[96,97]: Estrogen decline during menopause accelerates bone loss, increasing osteoporosis and fracture risk. HRT improves bone density, while bisphosphonates like alendronate and zoledronic acid, along with denosumab, offer alternatives. SERMs such as raloxifene enhance bone health and lower breast cancer

risk. These treatments strengthen bones and reduce fracture incidence effectively.

4. Improved Vaginal and Urinary Health[98 – 100]: Pharmacotherapy helps manage genitourinary symptoms of menopause, including vaginal dryness and urinary urgency. Vaginal estrogen therapy restores the vaginal epithelium, improves lubrication, and strengthens the urethral lining. Non-hormonal options like moisturizers and lubricants offer relief for those avoiding estrogen. These treatments enhance comfort and reduce urinary discomfort in menopausal women.

5. Cardiovascular Health[101,102]: Menopause increases cardiovascular risks due to estrogen deficiency, affecting lipid metabolism and vascular function. Early HRT improves lipid profiles and reduces arterial stiffness, but its benefits decline with age. Delayed initiation or pre-existing heart conditions may limit effectiveness, requiring alternative strategies for cardiovascular protection and symptom management in menopausal women.

6. Enhanced Sleep Quality[103-106]: Menopausal sleep disturbances worsen with vasomotor symptoms and mood disorders. HRT reduces night sweats, while SSRIs, SNRIs, and gabapentin help anxiety, depression, and pain, improving sleep quality, duration, and overall well-being.

7. Prevention of Long-term Health Risks[107]: Pharmacotherapy during menopause helps reduce long-term health risks linked to hormonal decline. HRT lowers osteoporosis-related fracture risk and may delay cardiovascular diseases if started early. SERMs like raloxifene protect bone health and reduce estrogen receptor-positive breast cancer risk. These benefits make pharmacotherapy crucial for managing symptoms and preventing future complications.

8. Personalized Symptom Management[108]: Pharmacotherapy adapts to individual needs, combining hormonal, non-hormonal, and lifestyle treatments for personalized menopausal care, ensuring safe, effective symptom management based on severity, risk factors, and personal preferences.

Pharmacotherapy is vital for managing perimenopausal and menopausal symptoms, but careful assessment of risks is crucial. Individual responses vary, and hormone replacement therapy (HRT) carries potential risks like breast tenderness, bloating, headaches, mood changes, and an increased risk of certain cancers. Non-hormonal treatments and bone health medications also have side effects, necessitating personalized, well-monitored treatment to ensure safety and effectiveness.

RECENT ADVANCES

In recent years, advances in pharmacotherapy have provided innovative options for managing perimenopausal and menopausal symptoms. These developments focus on improving efficacy, reducing side effects, and offering tailored approaches to address individual needs. Below are the key recent advancements:

1. Tissue-Selective Estrogen Complexes (TSECs): TSECs combine estrogen with drugs like bazedoxifene to relieve vasomotor symptoms, support bone health, and reduce endometrial hyperplasia risk, offering a safer alternative for women intolerant to progestins[109,110].

2. Neurokinin Receptor Antagonists: Neurokinin-3 receptor antagonists like fezolinetant offer non-hormonal relief for vasomotor symptoms by targeting hypothalamic pathways, benefiting women who cannot use hormones and showing efficacy with minimal side effects[111-114].

3. Advances in Hormone Replacement Therapy (HRT): Modern HRT uses low-dose transdermal estrogen and micronized progesterone for safer, steady hormone levels, reducing thromboembolism, breast cancer, and cardiovascular risks, while ultra-low-dose formulations minimize adverse effects[115,116].

5. Personalized Medicine and Genetic Testing: Advances in pharmacogenomics have opened the door to personalized medicine, where genetic testing helps determine the most suitable therapies based on an individual's genetic profile. This approach minimizes adverse effects and maximizes treatment efficacy, ensuring a tailored approach to managing menopausal symptoms[117].

CONCLUSION

Perimenopause and menopause are natural phases in a woman's life that bring significant hormonal changes, impacting everything from mood and bone health to heart health and vasomotor symptoms. Managing these shifts requires a tailored approach, blending medications and lifestyle changes. Hormone replacement therapy (HRT) is the most effective treatment, but for those who cannot use hormones, alternatives like SSRIs, SNRIs, gabapentin, and clonidine provide relief. Innovative therapies such as neurokinin receptor antagonists and stellate ganglion block (SGB) show great promise for easing symptoms. Alongside treatments, adopting a healthy lifestyle—balanced nutrition, regular exercise, stress management, and quitting smoking—can greatly improve overall well-being. While medications ease symptoms, a personalized care plan, considering each woman's health history and individual needs, is key. Individual risk factors due to prolonged pharmacotherapy should also be considered. With ongoing research, new and safer treatment options continue to emerge, empowering women to navigate menopause with greater ease and confidence.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. www.mayoclinic.org [INTERNET]. Perimenopause (cited 2023 May 2). Available from: https://www.mayoclinic.org/diseases-conditions/perimenopause/symptoms-causes/syc-20354666.
2. Harlow SD, Gass M, Hall JE, et al. Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab. 2012;97:1159–1168.
3. www.womenshealth.gov [INTERNET]. Menopause. Office on Women's Health. 22 February 2021. (cited 2023 May 2) Available from www.womenshealth.gov
4. Peacock K, Carlson K, Ketvertis KM. Menopause [INTERNET]. Treasure Island (FL): StatPearls Publishing; 2025 Jan [cited 2025 Feb 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279311/
5. International Menopause Society. World Menopause Day [INTERNET]. Bristol (UK): International Menopause Society; [cited 2025 Feb 15]. Available from: https://www.imsociety.org/education/world-menopause-day/?v=13b5bfe96f3e
6. Kirchengast S. Menopause: a biocultural perspective. Med Anthropol Q. 2008;21(4):414-6.
7. Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). Climacteric : the journal of the International Menopause Society. 2001 Dec;4(4):267–72.
8. Edwards H, Duchesne A, Au AS, Einstein G. The many menopauses: searching the cognitive research literature for menopause types. Menopause. 2019 Jan;26(1):45-65.
9. Shadyab AH, Macera CA, Shaffer RA, Jain S, Gallo LC, Gass ML, et al. Ages at menarche and menopause and reproductive lifespan as predictors of exceptional longevity in women: the Women's Health Initiative. Menopause 2017; 24:35–44.
10. *Massart F, Reginster JY, Brandi ML.* "Genetics of menopause-associated diseases". *Maturitas. 2002; 40 (2): 103–16.*
11. Hill K (1996). "The demography of menopause". Maturitas. 23 (2): 113–27.
12. Palacios S, Henderson VW, Siseles N, Tan D, Villaseca P (2010). "Age of menopause and impact of climacteric symptoms by geographical region". Climacteric. 13 (5): 419 – 28.
13. Green R, Santoro N (2009). "Menopausal symptoms and ethnicity: the Study of Women's Health Across the Nation". Womens Health (Lond). 5 (2): 127–33.
14. Dennerstein L, Dudley EC, Hopper JL, Guthrie JR, Burger HG. A prospective population-based study of menopausal symptoms. Obstet Gynecol 2000;96:351–358.
15. Freeman EW, Sammel MD, Sanders RJ. Risk of long-term hot flashes after natural menopause: Evidence from the Penn Ovarian Aging Study cohort. Menopause 2014;21:924–932.
16. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med 2015;175:531–539.
17. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. Maturitas 1992;14:103–115. 15. Matthews KA, Wing RR, Kuller LH, Meilahn EN, Plantinga P. Influence of the perimenopause on cardiovascular risk factors and symptoms of middle-aged healthy women. Arch Intern Med 1994;154:2349–2355.
18. Hale GE, Zhao X, Hughes CL, Burger HG, Robertson DM, Fraser IS. Endocrine features of menstrual cycles in middle and late reproductive age and the menopausal transition classified according to the Staging of Reproductive Aging Workshop (STRAW) staging system. J Clin Endocrinol Metab. 2007;92:3060–3067.
19. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44:291–303.
20. Bastian LA, Smith CM, Nanda K. Is this woman perimenopausal? JAMA. 2003;289:895–902. doi: 10.1001/jama.289.7.895.
21. Santoro N, Cedars M, Hansen K. AMH, FSH and AFC: The ABC's of ovarian reserve testing for the generalist. ACOG Update 2015;41.
22. www.pennmedicine.org [INTERNET]. The Change Before the Change: 9 Questions About Perimenopause. (cited 2023 May - 4) Available from https://www.penmedicine.org
23. www.health.harvard.edu [INTERNET]. Perimenopause: Rocky road to menopause. (cited 2023 May – 5) Available from https://www.health.harvard.edu/womens-health/perimenopause-rocky-road-to-menopause.
24. my.clevelandclinic.org[INTERNET]. Perimenopause (cited 2023 May – 5) Available from https://my.clevelandclinic.org/health/diseases/21608-perimenopause
25. www.webmd.com [INTERNET]. Perimenopause (cited 2023 May – 5) Available from https://www.webmd.com/menopause/guide/guide-perimenopause
26. www.nhs.uk [INTERNET]. Menopause (cited 2023 May – 6) Available from https://www.nhs.uk/conditions/menopause/symptoms
27. American Heart Association. Menopause and heart disease [Internet]. Updated 2017 Jun 23 [cited 2025 Feb 15]. Available from: www.heart.org.
28. Manouchehr Saljoughian. Menopause: Changes and Challenges. US Pharm. 2018;43(1):13-16.
29. Grady D, Barrett-Connor E. Menopause. In L Goldman, A Shafer, eds., Goldman's Cecil Medicine, 24th ed. Philadelphia, PA: Saunders. 2012;1565-1571.
30. Nelson HD. Menopause. Lancet. 2008;371:760-770.
31. Al-Safi ZA, Santoro N. Menopausal hormone therapy and menopausal symptoms. Fertil Steril. 2014;101:905-915.
32. www.theskintoloveclinic.co.uk [INTERNET]. 22 Signs Menopause has Started (cited 6 May 2023) Available from https://www.theskintoloveclinic.co.uk/blog/22-signs-menopause-has-started.
33. American Society for Reproductive Medicine. Menopausal transition (perimenopause): what is it? [INTERNET]. Updated 2015 [cited 2023 May 26]. Available from: https://www.reproductivefacts.org

34. Delamater L, Santoro N. Management of the Perimenopause. Clin Obstet Gynecol. 2018 Sep;61(3):419-432.

35. Burger HG. Diagnostic role of follicle-stimulating hormone (FSH) measurements during the menopausal transition – an analysis of FSH, estradiol and inhibin. Eur J Endocrinol 1994; 130: 38–42.

36. Burger HG, Dudley E, Mamers P, Groome N, Robertson DM. Early follicular phase serum FSH as a function of age: the roles of inhibin B, inhibin A and estradiol. Climacteric 2000; 3: 17–24.

37. Soules MR, Battaglia DE, Klein NA. Inhibin and reproductive aging in women. Maturitas 1998; 30: 193–204.

38. Robertson DM, Cahir N, Findlay JK, Burger HG, Groome N. The biological and immunological characterization of inhibin A and B forms in human follicular fluid and plasma. J Clin Endocrinol Metab 1997; 82: 889–96.

39. Welt CK, Smith ZA, Pauler DK, Hall JE. Differential regulation of inhibin A and inhibin B by luteinizing hormone, follicle stimulating hormone, and stage of follicle development. J Clin Endocrinol Metab 2001; 86: 2531–7.

40. Danforth DR, Arbogast LK, Mroueh J, Kim MH, Kennard EA, Seifer DB et al. Dimeric inhibin: a direct marker of ovarian aging. Fertil Steril 1998; 70: 119–23.

41. Kumar P, Magon N. Hormones in pregnancy. Niger Med J. 2012 Oct;53(4):179-83.

42. Rzeszowska M, Leszcz A, Putowski L, Hałabiś M, Tkaczuk-Włach J, Kotarski J, Polak G (2016). "Anti-Müllerian hormone: structure, properties and appliance". Ginekologia Polska. 87 (9): 669–674.

43. British Menopause Society. Nutrition and menopause [INTERNET]. London: British Menopause Society; 2022 Sep [cited 2023 Aug]. Available from: https://www.nutrition.org.uk/

44. Abrowska-Galas M, Dąbrowska J, Ptaszkowski K, Plinta R. High Physical Activity Level May Reduce Menopausal Symptoms. Medicina (Kaunas).2019;55(8):466.

45. Chopra S, Sharma KA, Ranjan P, Malhotra A, Vikram NK, Kumari A, et al. Weight Management Module for Perimenopausal Women: A Practical Guide for Gynecologists. J Midlife Health.2019;10(4):165-172.

46. Wong C, Yip BH, Gao T, Lam KYY, Woo DMS, Yip ALK, et al. Mindfulness-Based Stress Reduction (MBSR) or Psychoeducation for the Reduction of Menopausal Symptoms: A Randomized, Controlled Clinical Trial. Sci Rep.2018;8(1):6609.

47. Kline CE, Irish LA, Krafty RT, Sternfeld B, Kravitz HM, Buysse DJ, et al. Consistently high sports/exercise activity is associated with better sleep quality, continuity and depth in midlife women: the SWAN sleep study. Sleep.2013;36(9):1279-88.

48. Perry S. Menopause and dehydration: drink more water [INTERNET]. Gennev; 2019 May 21 [cited 2023 Aug]. Available from: https://www.gennev.com/education/menopause-and-dehydration

49. McVay MA, Copeland AL. Smoking cessation in peri- and postmenopausal women: a review. Exp Clin Psychopharmacol. 2011;19(3):192-202.

50. Freeman JR, Whitcomb BW, Purdue-Smithe AC, Manson JE, Langton CR, Hankinson SE, et al. Is Alcohol Consumption Associated With Risk of Early Menopause? Am J Epidemiol. 2021;190(12):2612-617.

51. aumova I, Castelo-Branco C. Current treatment options for postmenopausal vaginal atrophy. Int J Womens Health. 2018 Jul 31;10:387-395.

52. www.whmcenter.com[INTERNET]. Women's Health and Menopause Center .The Benefits of Menopause Screening and How to Do It. [Updated 2023, cited 2023 September]. Available from: https://www.whmcenter.com

53. Polat F, Orhan I, Şimşek Küçükkelepçe D. Does social support affect menopausal symptoms in menopausal women? Perspect Psychiatr Care. 2022 Jul;58(3):1062-1070.

54. Valdes A, Bajaj T. Estrogen therapy [INTERNET]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 Jan– [updated 2023 May 22; cited 2025 Feb 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK541051/

55. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. Hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017 Jul. 24 (7):728-753.

56. Wang Y, Sun C. Association of hormone preparations with bone mineral density, osteopenia, and osteoporosis in postmenopausal women: data from National Health and Nutrition Examination Survey 1999-2018. *Menopause*. 2023 Jun 1. 30 (6):591-8.

57. Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Long-term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2017 Jan 17;1(1):CD004143.

58. Nachtigall LE, Nachtigall RH, Nachtigall RD, Beckman EM. Estrogen replacement therapy II: a prospective study in the relationship to carcinoma and cardiovascular and metabolic problems. Obstetrics and Gynecology 1979;54(1):74-9.

59. Tierney MC, Oh P, Moineddin R, Greenblatt EM, Snow WG, Fisher RH, et al. A randomized double-blind trial of the effects of hormone therapy on delayed verbal recall in older women. Psychoneuroendocrinology 2009;34(7):1065-74.

60. Obel EB, Munk-Jensen N, Svenstrup B, Bennett P, Micic S, Henrik-Nielsen R, et al. A two-year double-blind controlled study of the clinical effect of combined and sequential postmenopausal replacement therapy and steroid metabolism during treatment. Maturitas 1993;16:13-21.

61. Holmberg L, Iversen OE, Rudenstam CM, Hammar M, Kumpulainen E, Jaskiewicz J, et al. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. Journal of the National Cancer Institute 2008;100(7):475–82.

62. Archer DF. Continuous combined hormone replacement therapy and endometrial hyperplasia. BMJ. 2002 Aug 3;325(7358):231-2.

63. Wells M, Sturdee DW, Barlow DH, Ulrich LG, O'Brien K, Campbell MJ, et al. Effect on endometrium of long term treatment with continuous combined oestrogen-progestogen replacement therapy: follow up study. BMJ. 2002;324:239–242.

64. Hill DA, Weiss NS, Beresford SA, Voigt LF, Daling JR, Stanford JL, et al. Continuous combined hormone replacement therapy and risk of endometrial cancer. Am J Obstet Gynecol. 2000;183:1456–1461.

65. Guzic-Salobir B, Keber I, Seljeflot I, Arnesen H, Vrabic L. Combined hormone replacement therapy improves endothelial function in healthy postmenopausal women. J Intern Med. 2001 Dec;250(6):508-15.

66. Al-Azzawi F, Wahab M, Habiba M, Akkad A, Mason T. Continuous combined hormone replacement therapy compared with tibolone. Obstet Gynecol. 1999 Feb;93(2):258-64.

67. itkin J, Smetnik VP, Vadász P, Mustonen M, Salminen K, Ylikangas S, et al. Continuous combined hormone replacement therapy relieves climacteric symptoms and improves health-related quality of life in early postmenopausal women. Menopause Int. 2007 Sep;13(3):116-23.

68. Lipov EG, Lipov S, Joshi JR, Santucci VD, Slavin KV, Beck Vigue SG. Stellate ganglion block may relieve hot flashes by interrupting the sympathetic nervous system. Med Hypotheses (2007) 69(4):758–63.

69. Haest K, Kumar A, Van Calster B, Leunen K, Smeets A, Amant F, et al. Stellate ganglion block for the management of hot flashes and sleep disturbances in breast cancer survivors: an uncontrolled experimental study with 24 weeks of follow-up. Ann Oncol (2012) 23(6):1449–54.

70. Narouze S. Ultrasound-guided stellate ganglion block: safety and efficacy. Curr Pain headache Rep (2014) 18(6):424.

71. Lipov EG, Joshi JR, Sanders S, Slavin KV. A unifying theory linking the prolonged efficacy of the stellate ganglion block for the treatment of chronic regional pain syndrome (CRPS), hot flashes, and posttraumatic stress disorder (PTSD). Med Hypotheses (2009) 72(6):657–61.

72. Yan M, Liu X, Wang L, Tao W, Zhang X, Wang S, et al. Chinese expert consensus on stellate ganglion block therapy, (2022 edition). Chin J Painol (2022) 18(03):293–301.

73. Guttuso T Jr. Stellate ganglion block for treating hot flashes: a viable treatment option or sham procedure? Maturitas (2013) 76(3):221–4.

74. Maki PM, Rubin LH, Savarese A, Drogos L, Shulman LP, Banuvar S, et al. Stellate ganglion blockade and verbal memory in midlife women: Evidence from a randomized trial. Maturitas (2016) 92:123–9.

75. Walega DR, Rubin LH, Banuvar S, Shulman LP, Maki PM. Effects of stellate ganglion block on vasomotor symptoms: findings from a randomized, controlled clinical trial in postmenopausal women. Menopause (New York NY) (2014) 21(8):807.

76. Li Y, Chang J, Shi G, Zhang W, Wang H, Wei L, et al. Effects of stellate ganglion block on perimenopausal hot flashes: a randomized controlled trial. Front. Endocrinol. 2023;14:1293358.

77. 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. Archives of General Psychiatry 2006;63(4):385-90.

78. Karanth L, Chuni N, Nair NS. Antidepressants for menopausal symptoms. Cochrane Database Syst Rev. 2019 Sep 12;2019(9):CD013417.

79. Azizi M, Khani S, Kamali M, Elyasi F. The Efficacy and Safety of Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors in the Treatment of Menopausal Hot Flashes: A Systematic Review of Clinical Trials. Iran J Med Sci. 2022 May;47(3):173-193.

80. Chiu CT, Wang Z, Hunsberger JG, Chuang DM. Therapeutic potential of mood stabilizers lithium and valproic acid: beyond bipolar disorder. Pharmacol Rev. 2013 Jan 8;65(1):105-42.

81. North American Menopause Society. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. Menopause (New York, N.Y.) 2015;22(11):1155-74.

82. Shan D, Zou L, Liu X, Shen Y, Cai Y, Zhang J. Efficacy and safety of gabapentin and pregabalin in patients with vasomotor symptoms: a systematic review and meta-analysis. Am J Obstet Gynecol. 2020 Jun;222(6):564-579.

83. Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. Jama. 2006;295(17):2057–2071.

84. Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev. 2016 Aug 31;2016(8).

85. Krause M, Wheeler TL 2nd, Snyder TE, Richter HE. Local Effects of Vaginally Administered Estrogen Therapy: A Review. J Pelvic Med Surg. 2009 May;15(3):105-114.

86. Abraham A, Cohen A, Shane E. Premenopausal bone health: osteoporosis in premenopausal women. Clin Obstet Gynecol. 2013 Dec;56(4):722-9.

87. McClung MR. Denosumab for the treatment of osteoporosis. Osteoporos Sarcopenia. 2017 Mar;3(1):8-17.

88. Chen LR, Ko NY, Chen KH. Medical Treatment for Osteoporosis: From Molecular to Clinical Opinions. Int J Mol Sci. 2019 May 06;20(9).

89. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. 2014 Oct;25(10):2359-81.

90. Crandall CJ, Mehta JM, Manson JE. Management of Menopausal Symptoms: A Review. JAMA. 2023 Feb 7;329(5):405-420.

91. Herson M, Kulkarni J. Hormonal Agents for the Treatment of Depression Associated with the Menopause. Drugs Aging. 2022 Aug;39(8):607-618.

92. Parry BL. Optimal management of perimenopausal depression. Int J Womens Health. 2010 Aug 9;2:143-51.

93. Borozan S, Kamrul-Hasan ABM, Pappachan JM. Hormone replacement therapy for menopausal mood swings and sleep quality: The current evidence. World J Psychiatry. 2024 Oct 19;14(10):1605-1610.

94. Charde SH, Joshi A, Raut J. A Comprehensive Review on Postmenopausal Osteoporosis in Women. Cureus. 2023 Nov 9;15(11):e48582.

95. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. [Jun; 2023];Cummings SR, San Martin J, McClung MR, et al. N Engl J Med. 2009 361:756–765.

96. Angelou K, Grigoriadis T, Diakosavvas M, Zacharakis D, Athanasiou S. The Genitourinary Syndrome of Menopause: An Overview of the Recent Data. Cureus. 2020 Apr 8;12(4):e7586.

97. The recent review of the genitourinary syndrome of menopause. Kim H, Kang SY, Chung YJ, Kim JH, Kim MR. J Menopausal Med. 2015;21:65–71. doi: 10.6118/jmm.2015.21.2.65.

98. Recommendations for the management of postmenopausal vaginal atrophy. Sturdee DW, Panay N. Climacteric. 2010;13:509–522.

99. Raj A, Chakole S, Agrawal S, Gupta A, Khekade H, Prasad R, et al. The Impact of Menopause on Cardiovascular Aging: A Comprehensive Review of Androgen Influences. Cureus. 2023 Aug 16;15(8):e43569.

100. Roles of hormone replacement therapy and menopause on osteoarthritis and cardiovascular disease outcomes: a narrative review. Mei Y, Williams JS, Webb EK, Shea AK, MacDonald MJ, Al-Khazraji BK. Front Rehabil Sci. 2022;3:825147.

101. Baker FC, Lampio L, Saaresranta T, Polo-Kantola P. Sleep and Sleep Disorders in the Menopausal Transition. Sleep Med Clin. 2018 Sep;13(3):443-456.

102. Cintron D, Lipford M, Larrea-Mantilla L, Spencer-Bonilla G, Lloyd R, Gionfriddo MR, et al. Efficacy of menopausal hormone therapy on sleep quality: systematic review and meta-analysis. Endocrine. 2017;55(3):702–711.

103. Polo-Kantola P, Erkkola R, Helenius H, Irjala K, Polo O. When does estrogen replacement therapy improve sleep quality?. Am J Obstet Gynecol. 1998;178(5):1002–1009.

104. Welton AJ, Vickers MR, Kim J, Ford D, Lawton BA, MacLennan AH, et al. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. BMJ. 2008;337:a1190.

105. Mehta J, Kling JM, Manson JE. Risks, Benefits, and Treatment Modalities of Menopausal Hormone Therapy: Current Concepts. Front Endocrinol (Lausanne). 2021 Mar 26;12:564781.

106. Lee SR, Cho MK, Cho YJ, Chun S, Hong SH, Kyu Ri Hwang, et al. The 2020 Menopausal Hormone Therapy Guidelines. Academic Committee of the Korean Society of Menopause, J Menopausal Med. 2020 Aug;26(2):69-98.

107. Lee DY. Tissue-Selective Estrogen Complex and Breast. J Menopausal Med. 2020 Aug;26(2):99-103.

108. Pickar JH, Boucher M, Morgenstern D. Tissue selective estrogen complex (TSEC): a review. Menopause. 2018 Sep;25(9):1033-1045.

109. Johnson KA, Martin N, Nappi RE, Neal-Perry G, Shapiro M, Stute P, et al. Efficacy and safety of fezolinetant in moderate to severe vasomotor symptoms associated with menopause: a phase 3 RCT. J Clin Endocrinol Metab. 2023 Jul 14;108(8):1981-1997.

110. Pinkerton JV, Redick DL, Homewood LN, Kaunitz AM. Neurokinin Receptor Antagonist, Fezolinetant, for Treatment of Menopausal Vasomotor Symptoms. J Clin Endocrinol Metab. 2023 Oct 18;108(11):e1448-e1449.

111. Javernick JA. A Novel Nonhormonal Treatment for Vasomotor Symptoms of Menopause. Nurs Womens Health. 2024 Feb;28(1):80-84.

112. Akhtar SMM, Ali A, Khan MS, Khan V, Fareed A, Saleem SZ, et al . Efficacy and safety of fezolinetant for vasomotor symptoms in postmenopausal women: A systematic review and meta-analysis of randomized controlled trials. Int J Gynaecol Obstet. 2024 Sep;166(3):969-983.

113. Manson JE, Crandall CJ, Rossouw JE, Chlebowski RT, Anderson GL, Stefanick ML, et al. The Women's Health Initiative randomized trials and clinical practice: A review(link is external). JAMA; 2024 May 28;331(20):1748-1760.

114. Cagnacci A, Xholli A, Venier M. Ospemifene in the Management of Vulvar and Vaginal Atrophy: Focus on the Assessment of Patient Acceptability and Ease of Use. Patient Prefer Adherence. 2020 Jan 10;14:55-62.

115. Sadee W, Wang D, Hartmann K, Toland AE. Pharmacogenomics: Driving Personalized Medicine. Pharmacol Rev. 2023 Jul;75(4):789-814.

116. Gold EB, Colvin A, Avis N, Bromberger J, Greendale GA, Powell L, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: Study of Women's Health Across the Nation. Am J Public Health. 2006;96:1226–1235.

117. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. J Am Med Assoc 2013;310:1353–1368.