MENOPAUSE

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM – September 2023

To the CHI Menopause Clinical Guidance- Issued September 2020

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

AHA	American Heart Association
CBT	Cognitive-Behavioral Therapy
CEE	Conjugated Equine Estrogen
CHD	Coronary Heart Disease
CHI	Council of Health Insurance
CNGOF	Collège National des Gynécologues et Obstétriciens Français
CPG	Clinical Practice Guideline
CVD	Cardiovascular Disease
EMA	European Medicines Agency
ET	Estrogen Therapy
EPT	Estrogen-Progestin Therapy
FDA	Food and Drug Administration
FSAD	Female Sexual Arousal Disorder
GEMVi	Groupe d'Étude sur la Ménopause et le Vieillissement Hormonal
GSM	Genitourinary Symptoms of Menopause
HRT	Hormone Replacement Therapy
HSDD	Hypoactive Sexual Desire Disorder/Dysfunction
IDF	CHI Drug Formulary
NAMS	the North American Menopause Society
LE	Level of Evidence
SFDA	Saudi Food and Drug Authority
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
THM	Postmenopausal Hormone Therapy
VMS	Vasomotor Symptoms
VTE	Venous Thromboembolism
WHI	Women's Health Initiative

Executive Summary

Menopause is a significant phase in a woman's life that signals the conclusion of her reproductive years. It is typically diagnosed after 12 months of no menstrual periods. However, the period leading up to and immediately following menopause is called the menopausal transition, during which hormonal changes and symptoms occur. Furthermore, during the menopausal transition, a woman's ovaries become less responsive to gonadotropin stimulation. This reduced sensitivity is primarily due to a natural process called follicular attrition. Throughout a woman's life, some ovarian eggs (oocytes) undergo atresia, a form of cell death, leading to a decline in both the quantity and quality of follicles in the ovaries. This leads to women reaching their final menstruation and eventually permanent amenorrhea1.

Following menopause, a woman becomes unable to conceive naturally, though there are exceptional instances where specialized fertility treatments may allow pregnancy. For most women, menopause occurs between the ages of 45 and 55 years as a normal part of the aging process. The decline in ovarian follicular function and a decrease in circulating estrogen levels are the primary factors contributing to menopause.

The hormonal changes associated with menopause can affect physical, emotional, mental, and social well-being. The symptoms that postmenopausal women experience include vasomotor symptoms such as hot flushes and night sweats, vaginal dryness, pain during sexual intercourse and incontinence; difficulty sleeping/insomnia; and changes in mood, depression, and/or anxiety[2].

A study was conducted to evaluate Menopausal symptoms and quality of life among Saudi women visiting primary care clinics in Riyadh, Saudi Arabia. The average age at menopause was 48.3±3 years (median, 49 years). Among the reported symptoms, joint and muscle pain were the most common (80.7%), followed by physical and mental exhaustion (64.7%), and hot flushes and sweating (47.1%). Perimenopausal women experienced a higher prevalence of somatic and psychological symptoms compared to other groups. The overall quality-of-life score was higher in perimenopausal women, and the total score from the Menopause Rating Scale (MRS) indicated that the symptoms were mild in severity[3].

Long-term complications of menopause are associated with decreased estrogen and include cardiovascular disease as well as osteoporosis. In fact, coronary heart disease rates are 2 to 3 times higher in those that have reached menopause than those of the same age who have not. As for osteoporosis, it is thought to affect more than 250,000 menopausal and postmenopausal women in the United States. During menopause, women experience an increased rate of bone loss of 3% to 5% per year for 5 to 7 years. In the Women’s Health Institute trial, hormone replacement was chosen to decrease osteoporotic fractures. This and various other studies have

shown that hormone therapy is protective against bone loss. However, there are risks associated with the long-term use of hormone therapy, such as endometrial and breast cancer and deep vein thrombosis/pulmonary embolism. For this reason, several other approaches to decreasing the risk of osteoporosis and related injuries are encouraged. Among these approaches are smoking cessation, physical activity, calcium supplementation, and non-hormonal treatments such as bisphosphonates and denosumab[4]. Detailed treatment options for the management of osteoporosis are discussed in a separate CHI report.

Medical treatment is not required for menopause. Instead, the focus is on alleviating the signs and symptoms associated with menopause and addressing or controlling any chronic conditions that may develop as part of the aging process. Treatment options include mainly hormone therapy, low-dose antidepressants, gabapentin and pregabalin, clonidine, and fezolinetant.

CHI issued Menopause clinical guidance after thorough review of renowned international and national clinical guidelines in September 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations. Below is a description of sections that need updates.

This report functions as an addendum to the prior CHI Menopause clinical guidance and seeks to offer guidance for the effective management of **Menopause**. It provides an **update on the Menopause Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized being **the new guidelines that are added to the report** such as: **Global Consensus Position Statement** on the Use of Testosterone Therapy for Women **(2019)**, **The 2022** hormone therapy position statement of **The North American Menopause Society**, Menopause and risk of thromboembolic events, Postmenopausal women management: **CNGOF and GEMVi** clinical practice guidelines **(2021)**, J**apan Society of Obstetrics and Gynecology, Japan Society for Menopause and Women's Health 2017** guidelines for hormone replacement therapy, Clinical impact of **2020 American Heart Association statement on menopause and cardiovascular disease risk** and **Menopause Practice Standards by British Menopause Society (BMS) Royal College of Obstetricians and Gynaecologists (RCOG) Society for Endocrinology (SfE) Faculty of Sexual and Reproductive Health (FSRH) Faculty of Pharmaceutical Medicine (FPM) Royal Pharmaceutical Society (RPS) (2022).**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it can be concluded that ETHINYLESTRADIOL, NORGESTIMATE combination has been removed from the formulary and PROGESTERONE gel as well as capsules for oral use have been added to the list. There have been no changes or updates made to

any of the previously listed drugs in terms of drug information and prescribing edits since September 2020.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Menopause management.

Below is a table summarizing the major changes based on the different menopause guidelines used to issue this report:

Table 1. General Recommendations for the Management of Menopause

Management of Menopause		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Hormone therapy, either estrogen alone or in combination with a progestin, is regarded as the most effective medical treatment for managing menopausal symptoms.	I-A	SOGC CLINICAL PRACTICE GUIDELINE 2014[5]
The main therapeutic objective should be to use the suitable and often the lowest effective dosage of systemic estrogen therapy (ET) that aligns with treatment goals, offering advantages while minimizing risks for each individual woman.	Level III	The North American Menopause Society 2022[6]
Testosterone therapy, administered at doses similar to the natural levels observed in premenopausal women, has a positive impact on sexual function. It leads to an increase in satisfying sexual experiences beyond the effects observed with placebo or comparator therapy. Additionally, it improves various aspects of sexual function, such as desire, arousal, orgasmic function, pleasure, and sexual responsiveness, while reducing sexual concerns, including distress.	Level I, Grade A	Global Consensus Position Statement 2019[7]
Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine	N/A	NICE Guideline 2015[8]

reuptake inhibitors (SNRIs), or clonidine are not routinely recommended as the first-line treatment for vasomotor symptoms alone.		
Non-hormonal prescription therapies, such as specific antidepressant medications, gabapentin, and clonidine, may offer some relief from hot flashes, but they have their own set of side effects. These alternatives can be considered when hormone therapy is not advised or contraindicated.	Level I-B	SOGC CLINICAL PRACTICE GUIDELINE 2014[5]
Cognitive-behavioral therapy (CBT) can be employed to reduce feelings of low mood or anxiety that arise due to menopause.	N/A	NICE Guideline 2015[8]

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI hypertension report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

There are no updated guidelines for this indication since September 2020.

Table 2. Guidelines Requiring Revision

Guidelines requiring revision	
Old versions	**Updated versions**
Menopause: Diagnosis and Management **NICE** Guidelines Published 12 November 2015, Updated 5 December **2019**	N/A*
SOGC Clinical Practice Guideline Endometriosis: Managing Menopause **2014**	N/A*
Treatment of Symptoms of the Menopause: An **Endocrine Society** Clinical Practice Guideline **2015**	N/A*

**: No updated version available:* the existing version is the most recent one and no further updates or revisions have been made or released.

1.2 Additional Guidelines

This section includes the added guidelines to the previous CHI Menopause report, along with their recommendations.

Table 3. List of Additional Guidelines

Additional Guidelines
Global Consensus Position Statement on the Use of Testosterone Therapy for Women **(2019)**
The **2022** Hormone Therapy Position Statement of **The North American Menopause Society**
Menopause and Risk of Thromboembolic Events. Postmenopausal Women management: **CNGOF and GEMVi Clinical Practice Guidelines (2021)**
Japan Society of Obstetrics and Gynecology and Japan Society for Menopause and Women's Health 2017 Guidelines for Hormone Replacement Therapy
Clinical Impact of **2020 American Heart Association** Statement on Menopause and Cardiovascular Disease Risk
Menopause Practice Standards by **British Menopause Society (BMS) Royal College of Obstetricians and Gynaecologists (RCOG) Society for Endocrinology (SfE) Faculty of Sexual and Reproductive Health (FSRH) Faculty of Pharmaceutical Medicine (FPM) Royal Pharmaceutical Society (RPS) (2022)**

1.2.1 Global Consensus Position Statement on the Use of Testosterone Therapy for Women (2019)

The Global Consensus Position Statement on the Use of Testosterone Therapy for Women (2019)[7] introduced a set of recommendations accompanied by a grading scheme, outlined as follows:

Table 4. Global Consensus Position Statement Category of Evidence Classification

Category of evidence	
IA	Evidence for meta-analysis of randomized, controlled trials
IB	Evidence from at least one randomized, controlled trial
IIA	Evidence from at least one controlled study without randomization
IIB	Evidence from at least one other type of quasi-experimental study
III	Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Table 5. Global Consensus Position Statement Strength of Recommendation

Strength of Recommendation	
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated recommendation from category I evidence
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence or extrapolated recommendation from category I, II, or Ill evidence

- Testosterone can exert its effects in two ways: either by directly interacting with the androgen receptor through non-genomic androgenic action, or by converting into the stronger androgen dihydrotestosterone, and/or being transformed into estradiol and its metabolites through aromatization.
- Testosterone levels decrease throughout the reproductive years (Level IIB).
- In women, testosterone levels seem to remain stable after the age of 65, but it is not yet clear if this has any advantageous effects (Level IIB).
- Liquid/gas chromatography and tandem mass spectrometry assays provide highly accurate and reproducible measurements of total testosterone (Grade B).
- The primary emphasis in current research on testosterone physiology and clinical effects should be on measuring total testosterone as the primary biomarker, rather than "free" testosterone, since there is a lack of evidence supporting that "free" testosterone is the biologically active fraction of testosterone (Expert Opinion).
- Hypoactive sexual desire disorder/dysfunction (HSDD) and female sexual arousal disorder (FSAD) are separate conditions that need to be categorized independently when studying the effects of androgens on their clinical manifestations and treatment outcomes (Grade B).
- While HSDD and FSAD may share some similarities, they have different causes, risk factors, clinical characteristics, and responses to psychological and biological treatments (Grade B).

Recommendations regarding testosterone treatment of naturally or surgically postmenopausal women with HSDD, with/or without concurrent estrogen therapy

- Testosterone therapy, when administered at doses similar to physiological levels in premenopausal women, has a positive impact on sexual function. It leads to an increase in satisfying sexual events, exceeding the effects observed with placebo/comparator therapy. Additionally, it improves various aspects of sexual function, such as desire, arousal, orgasmic function, pleasure, and sexual responsiveness, while reducing sexual concerns, including sexual distress (Level I, Grade A).
- It is important to note that the studies assessing sexual function primarily included women diagnosed with HSDD or generalized FSD. Therefore, these recommendations may not apply to other subtypes of FSD or women without sexual dysfunction (Expert Opinion).

Recommendations regarding the effects of testosterone on wellbeing, mood, and cognition in postmenopausal women

- There is not enough evidence to back the use of testosterone for boosting cognitive performance or delaying cognitive decline in postmenopausal women (Insufficient).
- Based on the currently available data, testosterone therapy does not appear to have any impact on general wellbeing (Level I, Grade A).
- Testosterone might have a positive effect on wellbeing in premenopausal women, but the existing data are inconclusive (Level 1, Grade B).
- The available data do not demonstrate any effect of testosterone on alleviating depressed mood (Level I, Grade B).

Recommendations regarding the musculoskeletal effects of testosterone

- Based on the evidence available, there is no support for the idea that testosterone treatment has an effect on bone mineral density at the spine, total hip, or femoral neck after 12 months (Level I, Grade A).
- Studies have not shown any statistically significant impact of testosterone administered in physiological doses on lean body mass, total body fat, or muscle strength (Level I, Grade A).
- Expert opinion suggests that clinical trials are necessary to assess the influence of testosterone treatment on musculoskeletal tissues.

Recommendations regarding possible androgenic side effects of testosterone therapy

- Systemic testosterone therapy for postmenopausal women, when administered at doses similar to physiological levels found in premenopausal women, may lead to slight increases in acne and body/facial hair growth in certain individuals. However, it is not associated with alopecia (hair loss), clitoromegaly (enlargement of the clitoris), or voice changes (Level I, Grade A).

Recommendations regarding testosterone therapy and cardiovascular health

- Taking testosterone orally is linked to unfavorable lipid profiles, causing negative impacts on high-density lipoprotein-cholesterol and low-density lipoprotein-cholesterol levels. As a result, oral testosterone therapy is not recommended (Level I, Grade A).
- Research on nonoral testosterone therapies (such as percutaneous and injectable methods) at doses similar to physiological levels found in premenopausal women has not shown any statistically significant adverse effects on lipid profiles in the short term (Level I, Grade A).
- Testosterone therapy has not been associated with increases in blood pressure, blood glucose, or HbA1c levels (Level I, Grade A).
- There has been a non-significant trend indicating a potential increased risk of deep venous thrombosis with testosterone therapy. However, the role of concurrent estrogen therapy in this potential venous thrombosis risk needs further investigation (Level I, Grade A).

Recommendations regarding testosterone therapy and breast health

- Testosterone therapy does not lead to an increase in mammographic breast density (Level I, Grade A).
- The data currently available indicate that short-term transdermal testosterone therapy does not have an effect on the risk of developing breast cancer (Level I, Grade A).

Recommendations regarding current testosterone therapy and postmenopausal women

- The only well-supported reason for using testosterone in women is for the treatment of postmenopausal women diagnosed with HSDD following a comprehensive biopsychosocial evaluation (Level I, Grade A).
- There is a recognized gap in the availability and approval of testosterone treatments tailored specifically for women, with the goal of achieving

testosterone levels similar to those found in premenopausal women (Expert Opinion).

- If a suitable approved testosterone product specifically designed for females is not accessible, prescribing an approved male formulation off-label can be considered reasonable, if hormone concentrations are kept within the physiological range for females (Expert Opinion).
- It is not recommended to use any form of testosterone preparation that leads to higher-than-physiological levels of testosterone, such as pellets and injections (Expert Opinion).
- Before starting a trial of testosterone therapy for HSDD, a baseline total testosterone level should be measured, and a follow-up test should be conducted 3 to 6 weeks after initiating treatment (Level IIA, Grade C).
- Patients undergoing testosterone therapy should be regularly monitored for their clinical response to the treatment, and their serum total testosterone level should be checked every 6 months to detect any signs of androgen excess and potential overuse (Expert Opinion).
- If no improvement is observed within 6 months of treatment, it is recommended to discontinue the therapy (Level IB, Grade C).

Recommendations regarding other androgenic preparations

- For postmenopausal women with normal adrenal function, systemic dehydroepiandrosterone does not show substantial improvement in libido or sexual function and is not recommended for those with HSDD (Level IA, Grade A).
- The effectiveness of vaginal dehydroepiandrosterone for the treatment of HSDD has not been studied in the absence of vulvovaginal atrophy, and therefore, it cannot be recommended for such use (Expert Opinion).

1.2.2 The 2022 Hormone Therapy Position Statement of The North American Menopause Society

The 2022 hormone therapy position statement of The North American Menopause Society[6] introduced a set of recommendations accompanied by a grading scheme, outlined as follows:

Table 6. The North American Menopause Society Grading of Recommendations

Grading of recommendations	
Level I	Based on good and consistent scientific evidence
Level II	Based on limited or inconsistent scientific evidence
Level III	Based primarily on consensus and expert opinion

- The primary therapeutic goal should be to use the appropriate and often the lowest effective dose of systemic estrogen therapy (ET) that aligns with treatment objectives, providing benefits while minimizing risks for each individual woman (Level III).
- Various formulations, doses, and administration routes of hormone therapy have similarly high efficacy in relieving vasomotor symptoms (VMS) (Level I).
- Decisions regarding the formulation, dose, and administration route of hormone therapy should be tailored individually for each woman and should be periodically reevaluated (Level III).
- Different hormone therapy doses, formulations, and administration routes may have distinct effects on target organs, offering potential options to reduce risks (Level II).
- In general, the heightened absolute risks linked to estrogen-progestin therapy (EPT) and estrogen therapy (ET) are infrequent, occurring in fewer than 10 cases per 10,000 women per year. These risks encompass a higher likelihood of venous thromboembolism (VTE) and gallbladder disease. Additionally, EPT presents a rare elevated risk of stroke and breast cancer, and inadequate opposition of estrogen can result in an increased risk of endometrial hyperplasia and endometrial cancer. (Level I)
- For women under the age of 60, the absolute risks are decreased for all-cause mortality, fractures, diabetes mellitus (for both EPT and ET), and breast cancer (for ET). (Level I)
- To counteract the proliferative effects of systemic estrogen on the endometrium, selecting the appropriate formulation, dose, and administration route of progestogen is essential (Level I).
- Hormone therapy has received FDA approval for four specific indications: alleviation of moderate to severe vasomotor symptoms (VMS), prevention of osteoporosis in postmenopausal women, treatment of hypoestrogenism resulting from hypogonadism, bilateral oophorectomy (BO), or premature ovarian insufficiency (POI), and management of moderate to severe

vulvovaginal symptoms. In cases where there are no indications for systemic estrogen therapy, FDA guidance suggests the use of low-dose topical vaginal estrogen therapy for the treatment of genitourinary symptoms associated with menopause (Level I).

- Compounded bioidentical hormone therapy (estradiol, estrone, and micronized progesterone (MP)), raises safety issues due to limited government regulation and monitoring, the risk of overdosing or underdosing, the possibility of impurities and lack of sterility, inadequate scientific evidence regarding efficacy and safety, and the absence of a label clearly indicating potential risks (Level I).
- Compounded bioidentical hormones may be considered in specific situations, such as when there are allergies to ingredients present in government-approved formulations or when required dosages are not available in government-approved products (Level III).

Vasomotor symptoms

- Hormone therapy remains the preferred method for relieving vasomotor symptoms (VMS).
- For women without a uterus, estrogen-alone therapy can be used. (Level I)
- For women with a uterus, either estrogen-progestin therapy (EPT) or tissue-selective estrogen complex (TSEC) can be used to protect against endometrial neoplasia. (Level I)
- When deciding on the formulation, administration route, and dosage of hormone therapy for menopause symptom management, shared decision-making should be employed, considering symptom relief, adverse effects, and patient preferences. (Level III)
- The necessity of continued hormone therapy should be periodically assessed based on a woman's menopause symptoms, overall health, underlying medical conditions, risks, treatment goals, and personal preferences. (Level III)
- Taking 300 mg of micronized progesterone nightly has shown significant reduction in vasomotor symptoms (hot flashes and night sweats) and improved sleep when compared to placebo. Synthetic progestins have also demonstrated some benefit for VMS in certain studies. Long-term study results are lacking, and using progestogens without estrogen for these indications is considered off-label. (Level II)

Sleep disturbances

- Hormone therapy enhances sleep in women experiencing bothersome nighttime vasomotor symptoms (VMS) by reducing instances of nighttime awakenings. Additionally, estrogen may have some impact on sleep, unrelated to the effects of VMS. (Level II)

Genitourinary symptoms

- Low-dose vaginal estrogen therapy (ET) preparations are effective and generally safe for treating genitourinary symptoms of genitourinary syndrome of menopause (GSM). They have minimal systemic absorption and are preferred over systemic therapies when ET is solely used for managing genitourinary symptoms. (Level I)
- For women with breast cancer, prescribing low-dose vaginal estrogen therapy should be done in consultation with their oncologists. (Level III)
- When using low-dose vaginal estrogen, progestogen therapy is not required, although randomized controlled trial (RCT) data are lacking beyond a 1-year duration. (Level II)
- FDA-approved nonestrogen prescription therapies that improve vulvovaginal atrophy (VVA) in postmenopausal women include ospemifene and intravaginal dehydroepiandrosterone (DHEA). (Level I)

Urinary tract symptoms (including pelvic floor disorders)

- Systemic hormone therapy does not lead to improvements in urinary incontinence and might even increase the incidence of stress urinary incontinence. (Level I)
- Low-dose vaginal estrogen therapy (ET) may offer advantages for urinary symptoms, including preventing recurrent urinary tract infections (UTIs), managing overactive bladder, and urge incontinence. (Level II)
- Hormone therapy has not received FDA approval for any urinary health indication. (Level I)

Sexual function

- Both systemic hormone therapy and low-dose vaginal estrogen therapy (ET) have the effect of increasing lubrication, blood flow, and sensation in vaginal tissues. (Level I)
- Systemic hormone therapy, in general, does not independently improve sexual function, sexual interest, arousal, or orgasmic response, apart from its impact on genitourinary syndrome of menopause (GSM). (Level I)

- For women experiencing menopause symptoms and concerned about sexual function or libido, transdermal estrogen therapy may be preferable over oral estrogen therapy due to its minimal effect on sex hormone-binding globulin and free testosterone levels. (Level II)
- Low-dose vaginal estrogen therapy improves sexual function in postmenopausal women with GSM. (Level I)
- FDA-approved nonestrogen alternatives for dyspareunia include ospemifene and intravaginal dehydroepiandrosterone (DHEA). (Level I)

Primary Ovarian Insufficiency

- Women with premature ovarian insufficiency (POI) or experiencing premature or early menopause may face elevated risks of various health conditions, including fractures, cardiovascular disease (CVD), heart failure, diabetes mellitus (DM), overall mortality, persistent vasomotor symptoms (VMS), fertility loss, bone loss, genitourinary symptoms, sexual dysfunction, cognitive and mood changes, increased risk of dementia, open-angle glaucoma, depression, and reduced quality of life. (Level II)
- If there are no contraindications, hormone therapy is suggested to be used until at least the average age of menopause, which is around 52 years old. In healthy younger women, oral contraceptives are also an alternative for treatment. (Level II)
- Young women facing the risk of premature ovarian insufficiency (POI) should consider fertility preservation options and counseling. (Level III)
- For premenopausal women at average risk for ovarian cancer who require hysterectomy for non-cancerous reasons, it is advised to retain the ovaries (ovarian conservation). (Level II)

Skin, hair, and special senses

- Estrogen therapy administered during menopause seems to have positive effects on skin thickness, elasticity, and collagen. (Level II)
- Hormone therapy seems to lower the risk of neovascular and soft drusen age-related macular degeneration, but it does not affect early or late-stage macular degeneration. (Level II)
- Estrogen therapy appears to decrease intraocular pressure and potentially reduce the risk of open-angle glaucoma in Black women. (Level II)

Osteoporosis

- Hormone therapy is effective in preventing bone loss in healthy postmenopausal women, and its impact on bone density is dose-related. (Level I)
- In healthy postmenopausal women, hormone therapy reduces the risk of fractures. (Level I)
- Rapid bone loss occurs when hormone therapy is discontinued, but the Women's Health Initiative (WHI) study did not observe an excess of fractures after discontinuation. (Level I)
- Hormone therapy is FDA-approved for preventing bone loss but not for the treatment of osteoporosis. (Level I)
- In women younger than 60 years of age or within 10 years of menopause onset, systemic hormone therapy is appropriate to safeguard against bone loss if there are no contraindications. (Level I)
- For women with premature menopause and no prior fragility fracture or osteoporosis, the best approach is to use hormone therapy or oral contraceptives to prevent bone density loss and reduce fracture risk until the average age of menopause, at which point treatment may be reevaluated. Other bone-specific treatments should be considered only if contraindicated. (Level II)

Sarcopenia

- Preclinical investigations indicate a potential advantage of estrogen therapy (ET) when used in conjunction with exercise to prevent muscle mass loss, strength decline, and performance deterioration. However, such outcomes have not been demonstrated in clinical trials. (Level II)

Gallbladder and Liver

- The use of estrogen therapy (ET) and estrogen-progestin therapy (EPT) is associated with an elevated risk of gallstones, cholecystitis, and cholecystectomy. (Level I)

Metabolic syndrome and diabetes

- Hormone therapy leads to a substantial decrease in the incidence of new-onset type 2 diabetes mellitus (DM), but it is not officially approved by the government for this purpose. (Level I)

- For otherwise healthy women with preexisting type 2 DM, hormone therapy is not contraindicated and may be beneficial in terms of glycemic control when used to manage menopause symptoms. (Level II)
- While hormone therapy might assist in mitigating abdominal adipose accumulation and weight gain related to menopause transition, the effect is modest. (Level II)

Cognition

- Until more conclusive evidence is available, hormone therapy is not advised at any age as a preventive or treatment measure for cognitive decline or dementia. (Level I)
- Estrogen therapy might offer cognitive advantages if started promptly after hysterectomy with bilateral oophorectomy. However, during the early natural postmenopause period, hormone therapy appears to have neutral effects on cognitive function. (Level II)

Depression

- There is evidence suggesting that estrogen therapy (ET) exhibits antidepressant effects of comparable magnitude to those observed with antidepressant agents when given to perimenopausal women experiencing depression, with or without concurrent vasomotor symptoms (VMS). (Level II)
- Estrogen therapy (ET) is not effective in treating depressive disorders in postmenopausal women. However, there is evidence suggesting a potential window of opportunity for using ET effectively to manage depressive disorders during the perimenopause period. (Level II)
- Some evidence indicates that ET can improve mood and enhance overall well-being in nondepressed perimenopausal women. (Level II)
- The use of transdermal estradiol with intermittent progestogen may prevent the onset of depressive symptoms in euthymic perimenopausal women. However, there is insufficient evidence to recommend estrogen-based therapies for preventing depression in asymptomatic perimenopausal or postmenopausal women, and the risks and benefits must be carefully evaluated. (Level II)

Cardiovascular disease and all-cause mortality

- For healthy symptomatic women below 60 years of age or within 10 years of menopause onset, the beneficial effects of hormone therapy on coronary heart disease (CHD) and all-cause mortality should be weighed against

potential rare increases in risks of breast cancer, venous thromboembolism (VTE), and stroke. (Level I)

- Hormone therapy is not approved by the government for primary or secondary cardioprotection. (Level I)
- When considering the initiation of hormone therapy, personal and familial risks of cardiovascular disease (CVD), stroke, VTE, and breast cancer should be considered. (Level III)
- The effects of hormone therapy on CHD may vary based on when it is started in relation to a woman's age or time since menopause onset. (Level I)
- In randomized, controlled trials, initiating hormone therapy in recently postmenopausal women either reduced or had no effect on the progression of subclinical atherosclerosis and coronary artery calcification. (Level I)
- Observational data and meta-analyses demonstrate a reduced risk of CHD in women who start hormone therapy before the age of 60 years or within 10 years of menopause onset. However, meta-analyses show no significant effect of hormone therapy on CHD after excluding open-label trials. (Level II)
- Women who begin hormone therapy after the age of 60 years or more than 10 or 20 years from menopause onset face higher absolute risks of CHD, VTE, and stroke compared to women who start hormone therapy during early menopause. (Level I)

Breast Cancer

- Women should receive counseling regarding the risk of breast cancer associated with hormone therapy. It is important to put the data into perspective, as the risk is similar to that of modifiable risk factors like consuming two alcoholic beverages daily, being obese, and having low physical activity. (Level III)
- The impact of hormone therapy on breast cancer risk may vary depending on factors such as the type of hormone therapy, duration of use, regimen, prior exposure to hormones, and individual characteristics. (Level II)
- Different hormone therapy regimens might be linked to increased breast density, potentially leading to difficulties in mammographic interpretation. This could result in the need for more mammograms or breast biopsies and may lead to a potential delay in breast cancer diagnosis. (Level II)
- Most of the available data do not indicate an additional effect of hormone therapy use on breast cancer incidence when considering factors such as age, family history of breast cancer, genetic risk of breast cancer, benign breast disease, and personal breast cancer risk factors. (Level II)

- There is insufficient data to assess the risk of breast cancer with newer therapies, like tissue-selective estrogen complexes (TSECs), including BZA plus CEE. (Level II)
- Observational evidence suggests that hormone therapy use does not further increase breast cancer risk in women at high risk due to a family history of breast cancer or after undergoing bilateral salpingo-oophorectomy (BSO) for BRCA1 or BRCA2 genetic variants. (Level II)
- For breast cancer survivors, systemic hormone therapy is generally not recommended. However, it may be considered for women with severe vasomotor symptoms (VMS) that are unresponsive to nonhormone options, in consultation with their oncologists and through shared decision-making. (Level III)
- For breast cancer survivors experiencing genitourinary symptoms of menopause (GSM), low-dose vaginal estrogen therapy (ET) or dehydroepiandrosterone (DHEA) may be considered, with consultation with their oncologists, if bothersome symptoms persist after trying nonhormone therapy. Concerns are heightened when considering low-dose vaginal ET for women on aromatase inhibitors (AIs). (Level III)
- Regular breast cancer surveillance is recommended for all postmenopausal women according to current breast cancer screening guidelines, including those using hormone therapy. (Level I)

Endometrial cancer

- Unopposed systemic estrogen therapy (ET) in postmenopausal women with an intact uterus increases the risk of endometrial cancer, making it crucial to use adequate progestogen alongside it. (Level I)
- Low-dose vaginal estrogen therapy (ET) does not seem to elevate the risk of endometrial cancer, although trials with endometrial biopsy endpoints have been limited to a duration of 1 year. (Level II)
- Hormone therapy may be considered as an option for treating bothersome menopause symptoms in women who have surgically treated, early stage, low-grade endometrial cancer. This decision should be made in consultation with the woman's oncologist if nonhormone therapies have been ineffective. (Level II)
- Systemic hormone therapy is not recommended for use in cases of high-grade, advanced-stage endometrial cancers or with endometrial stromal sarcomas or leiomyosarcomas. (Level II)

Ovarian cancer

- Taking oral contraceptives is linked to a substantial decrease in the risk of ovarian cancer. (Level I)
- In observational studies, current and recent use of hormone therapy is associated with a slight but statistically significant risk of ovarian cancer, primarily for the serous type. However, women enrolled in the WHI who were randomized to estrogen-progestin therapy (EPT) did not experience an increased risk of ovarian cancer. (Level II)
- In women with a history of ovarian cancer, the benefits of hormone therapy use generally outweigh the risks, particularly when dealing with bothersome vasomotor symptoms or early menopause. Nonetheless, hormone therapy is not recommended for women with hormone-dependent ovarian cancers, including granulosa-cell tumors and low-grade serous carcinoma. (Level II)

Colorectal cancer

- Observational studies indicate a lower occurrence of colorectal cancer in women currently using hormone therapy, leading to reduced mortality rates. (Level II)
- In the Women's Health Initiative (WHI) study, estrogen-progestin therapy (EPT) was found to reduce the risk of colorectal cancer, but not estrogen therapy (ET) alone. However, cancers detected in EPT users were diagnosed at a more advanced stage. There was no difference in colorectal cancer mortality with either EPT or ET. (Level I)

1.2.3 Menopause and Risk of Thromboembolic Events. Postmenopausal Women Management: CNGOF and GEMVi Clinical Practice Guidelines (2021)

The National College of French Gynecologists and Obstetricians (CNGOF) and the Study Group on Menopause and Hormonal Aging (GEMVi) published joint clinical guidelines on menopause and the risk of thromboembolic events[9]. They introduced a set of recommendations accompanied by a grading scheme, outlined as follows:

Table 7. CNGOF and GEMVi Clinical Practice Guidelines Level of Evidence

Level of evidence	
Level of evidence 1 (LE1)	• High-powered randomized controlled trials • Meta-analyses of randomized controlled trials • Decision analysis based on well-conducted studies
Level of evidence 2 (LE2)	• Underpowered randomized controlled trials • Well-conducted non-randomized controlled trials • Well-conducted prospective uncontrolled trials (e.g., cohort follow-up)
Level of evidence 3 (LE3)	• Case-control studies
Level of evidence 4 (LE4)	• Controlled trials with bias • Retrospective studies and clinical cases (series of patients). • Descriptive epidemiological studies (cross-sectional, longitudinal)

- The risk of venous thromboembolism (VTE) in the general population is increased by 1.7 times when using oral estrogens such as ethinylestradiol (ECE) and 17-β-estradiol, compared to placebo (Level of Evidence 1 - LE1). Specifically, the risk appears to be higher with ECE compared to 17-β-estradiol (Level of Evidence 2 - LE2).
- However, when using dermal estradiol, there is no apparent increase in the risk of VTE in the general population (LE2).
- The risk of VTE varies depending on the type of progestogen combined with hormone therapy (THM). When the THM includes dermal estradiol, the risk of VTE appears to be neutral for users of micronized progesterone and pregnane derivatives but increased for users of norpregnane derivatives in the general population (LE2).
- For women with a personal history of VTE (deep vein thrombosis or pulmonary embolism), HRT with oral estrogen therapy increases the risk of VTE recurrence (LE1). However, HRT using cutaneous estrogen therapy seems to have a neutral effect on the risk of VTE recurrence (LE3).
- In women with a factor V Leiden mutation or a prothrombin G20210A mutation, HRT with oral estrogen therapy increases the risk of VTE (LE1). On the other hand, THM with cutaneous estrogen therapy does not seem to affect the risk of VTE (LE3).

- In obese women, the use of THM with oral estrogen therapy increases the risk of VTE (LE1). However, for dermal estradiol users, there does not seem to be an increased risk of VTE, regardless of their body mass index (BMI) (LE2).
- Using vaginal estradiol as part of the treatment for vulvovaginal atrophy does not appear to increase the risk of VTE (LE3).

1.2.4 Japan Society of Obstetrics and Gynecology and Japan Society for Menopause and Women's Health 2017 Guidelines for Hormone Replacement Therapy

Japan Society of Obstetrics and Gynecology and Japan Society for Menopause and Women's Health 2017 guidelines for hormone replacement therapy[10] introduced a set of recommendations accompanied by a grading scheme, outlined as follows:

Table 8. Japan Society of Obstetrics and Gynecology and Japan Society for Menopause and Women's Health Guidelines Quality of Evidence

Quality of Evidence	
(+ + + +)	High
(+ + + –)	Moderate
(+ + – –)	Low
(+ – – –)	Very low

Table 9. Japan Society of Obstetrics and Gynecology and Japan Society for Menopause and Women's Health Guidelines Strength of Recommendation

Strength of Recommendation	
1	Strong or 'we recommend' or 'we recommend against'
2	Weak or 'we suggest' or 'we suggest against'

Characteristics of HRT and General Precautions for Use

- When used appropriately, hormone replacement therapy (HRT) can be advantageous for enhancing or sustaining the quality of life in postmenopausal women. However, there might be instances where it could lead to adverse effects. It is essential to thoroughly evaluate the benefits and risks associated with HRT before considering its use.
- Progestogen is administered to prevent endometrial hyperplasia and the elevated risk of endometrial cancer that may occur during systemic estrogen

therapy. As a result, it is not necessary for women without a uterus or those receiving lower doses of vaginal estrogen.

- To mitigate the heightened risk of endometrial cancer, the combined use of estrogen and progestogen is essential for women with a uterus.

Expected effects of HRT

- Both oral and transdermal estrogen are effective in alleviating hot flashes.
- Conjugated equine estrogen (CEE) offers relief from a range of menopausal symptoms, including night sweats, sexual dysfunction, insomnia, vaginal dryness, memory loss, frequent urination, and psychological symptoms, in addition to hot flashes.
- When combined with medroxyprogesterone acetate (MPA), CEE enhances health-related quality of life.
- Estradiol (E2) is effective in improving sleep disorders, joint pain, and limb pain, along with alleviating hot flashes.
- Hormone replacement therapy (HRT) has the potential to prevent or alleviate joint pain. (Level of Recommendation: 2, Level of Evidence (+ + − −))

  HRT is considered effective for insomnia. (Level of Recommendation: 2, Level of Evidence (+ + + −))

  When organic diseases have been ruled out, hormone replacement therapy (HRT) has been found to be effective in addressing back pain, which is considered a symptom of menopausal disorder. (Level of Recommendation: 2, Level of Evidence (+ −−−))
- HRT does not directly impact pelvic organ prolapse, but it does improve related lower urinary tract symptoms, vaginal atrophy, and vaginal dryness. (Level of Recommendation: 2, Level of Evidence (+ + − −))

  HRT improves dyspareunia and vaginal lubrication. (Level of Recommendation: 1, Level of Evidence (+ + + −))

  The topical application of estrogen is beneficial in managing overactive bladder symptoms. (Level of Recommendation: 2, Level of Evidence (+ + + −))
- HRT can be used in smokers, but it is important to note that the beneficial effects may be reduced, and there could be an increase in adverse events. Therefore, it is essential to offer guidance on adopting appropriate lifestyle habits, including smoking cessation, alongside HRT. (Level of Recommendation: 2, Level of Evidence (+ + − −))

- HRT is possible for obese patients, although careful administration or conditional administration is necessary. (Level of Recommendation: 2, Level of Evidence (+ + − −))
- HRT is feasible for women with a history of endometriosis, but careful consideration should be given to the recurrence of clinical symptoms, the worsening or possible malignant transformation of the lesions. (Level of Recommendation: 1, Level of Evidence (+ + − −))
- HRT is possible for women with controlled high blood pressure. (Level of Recommendation: 2, Level of Evidence (+ + − −))
- HRT is possible for women with diabetes mellitus with satisfactorily controlled blood glucose and no arteriosclerotic disease. (Level of Recommendation: 2, Level of Evidence (+ + − −))
- HRT recommended for women with premature ovarian insufficiency (POI). (Level of Recommendation: 1, Level of Evidence (+ + − −))
- HRT is recommended for cervical cancer survivors. (Level of Recommendation: 1 Level of Evidence (+ + + −))
- HRT is recommended for ovarian cancer survivors. (Level of Recommendation: 1, Level of Evidence (+ + − −))
- HRT is possible for women with BRCA1/2 gene mutation for a short term. (Level of Recommendation: 1, Level of Evidence (+ + + −))

  HRT is recommended for women with no estrogen deficiency symptoms if there is a clear goal(s), with benefits outweighing risks. (Level of Recommendation: 1 Level of Evidence (+ −−−))

  Oral estriol monotherapy can be utilized in women with a uterus, but it is crucial to monitor for endometrial hyperplasia and genital bleeding. For long-term administration, it is generally advisable to consider the concurrent use of progestogen. (Level of Recommendation: 1, Level of Evidence (+ + − −))

  Bazedoxifene, when used together with conjugated estrogen, is known to offer endometrial protection, suggesting a potential alternative to progestogens. (Level of Recommendation: 2, Level of Evidence (+ + − −))

  HRT can be considered for initiation in women over the age of 60 if there is a clear medical indication, and if the potential benefits outweigh the associated risks. (Level of Recommendation: 2, Level of Evidence (+ + + −))
- There are no specific age limits or set time periods that restrict the continuation of HRT. (Level of Recommendation: 1, Level of Evidence (+ −−−)

1.2.5 Clinical Impact of 2020 American Heart Association Statement on Menopause and Cardiovascular Disease Risk

The following statements are the main recommendations retrieved from Clinical impact of 2020 American Heart Association statement on menopause and cardiovascular disease risk[11]:

Lifestyle interventions

Female patients going through menopause in midlife should receive regular counseling on lifestyle interventions designed to promote ideal cardiovascular health. Following the American Heart Association's Life's Simple 7 components, achieving ideal cardiovascular health involves implementing the following interventions:

- Smoking cessation
- Weight management to achieve an ideal body weight (body mass index < 25 kg/m2) ·
- Optimization of cholesterol levels: total cholesterol < 200 mg/dL, low density lipoprotein cholesterol (LDL-C) < 100 mg/dL, high density lipoprotein cholesterol (HDLC) > 50 mg/dL, triglycerides < 150 mg/dL, non–HDL-C < 130 mg/dL)
- Optimization of blood pressure levels (< 120/80 mmHg)
- Optimization of fasting blood glucose (goal < 100 mg/dL)
- Engaging in at least 150 min/week of moderate-intensity exercise or 75 minutes per week of vigorous exercise (or a combination of both) · A DASH (Dietary Approaches to Stop Hypertension) diet.

Aspirin use

Although not extensively covered in this scientific statement, previous American Heart Association (AHA) guidelines have stated that the use of aspirin for primary prevention of heart attack is not recommended in female patients who are under the age of 65 and do not have cardiac risk factors. This recommendation is based on a careful assessment of the potential risks and benefits of aspirin therapy in this specific population. It is essential for healthcare providers to consider individual patient characteristics and risk factors when making decisions about aspirin use for heart attack prevention.

Lipid-lowering interventions

- As mentioned previously, primary approaches for improving lipid levels in middle-aged female patients involve lifestyle adjustments like regular physical activity, achieving and sustaining a healthy body weight, refraining from smoking, and adopting a heart-healthy diet.
- The impact of omega-3 and omega-6 fatty acid supplementation or dietary consumption on reducing the risk of coronary heart disease, heart attacks, lowering total cholesterol levels, or decreasing rates of cardiovascular or overall mortality remains unclear in midlife women. This uncertainty leaves us uncertain about the potential effects, if any, of omega-3 and omega-6 fatty acids on preventing cardiovascular disease in this population.
- For both primary and secondary prevention, women with hypercholesterolemia and/or hypertriglyceridemia may contemplate incorporating omega-3 fatty acids into their diets through fish consumption or by taking capsules, such as eicosapentaenoic acid at a dose of 1800 mg per day.
- The use of HMG-CoA reductase inhibitors, commonly known as statins, for reducing the risk of cardiovascular disease in middle-aged women continues to be a subject of debate and controversy.
- The scientific statement from the American Heart Association (AHA) highlighted that evidence regarding the effectiveness of lipid-lowering medications for both primary and secondary prevention, as well as for enhancing survival in women, remains inconclusive. As of now, non-pharmacological approaches are considered the primary strategies for enhancing lipid profiles.
- Moreover, considering that diabetes is a recognized risk factor for cardiovascular disease (CVD), it is essential to acknowledge that some studies have indicated an elevated risk of diabetes in postmenopausal women who use statins.
- The most prevalent nonstatin therapies include bile acid sequestrants, cholesterol absorption inhibitors, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. These may be employed either alongside or as alternatives to statins for reducing cholesterol levels in specific patients. However, their use for primary cardiovascular disease prevention in both men and women remains uncertain. Consequently, sex-specific trials are needed to ascertain their effectiveness in this regard.

Supplements

- At present, there are no vitamin or antioxidant supplements recommended for either primary or secondary prevention of cardiovascular disease (CVD).

Menopausal hormone therapy

- There is limited data on how menopausal hormone therapy (HT) affects perimenopausal women's cardiometabolic health.
- The impact of HT on atherosclerosis and CVD event progression varies based on age and when HT is initiated.
- Currently, HT and selective estrogen receptor modulators are not recommended for primary or secondary CVD prevention in postmenopausal women.
- However, research suggests that early HT initiation in cases of premature or surgical menopause and within ten years of natural menopause may have cardiovascular benefits.
- Using HT to counter early estrogen loss is considered standard care, but individualized assessment is crucial.

1.2.6 Menopause Practice Standards by British Menopause Society (BMS) Royal College of Obstetricians and Gynaecologists (RCOG) Society for Endocrinology (SfE) Faculty of Sexual and Reproductive Health (FSRH) Faculty of Pharmaceutical Medicine (FPM) Royal Pharmaceutical Society (RPS) (2022)

The following statements are the main recommendations retrieved from Menopause Practice Standards by British Menopause Society (BMS) Royal College of Obstetricians and Gynaecologists (RCOG) Society for Endocrinology (SfE) Faculty of Sexual and Reproductive Health (FSRH) Faculty of Pharmaceutical Medicine (FPM) Royal Pharmaceutical Society (RPS) (2022)[12]:

- The diagnosis of perimenopause or menopause in women aged 45 years and over, who are experiencing menopausal symptoms, can typically be established based on their symptoms alone. Confirmatory blood tests (FSH, oestradiol) are generally unnecessary unless there is uncertainty about the diagnosis.
- Many women may encounter bothersome menopausal symptoms even when they are in the perimenopausal phase, which is the period leading up to menopause characterized by irregular menstrual cycles and possibly

menopausal symptoms. It is important to consider this when evaluating women's health.

- The most common symptoms experienced during menopause include:
    1. Vasomotor symptoms (hot flushes/night sweats).
    2. Cognitive symptoms and mood disorders (low mood, labile mood, anxiety, irritability, loss of confidence, low self-esteem, difficulties with short-term concentration and memory ('Brain fog'), and difficulties in multi-tasking).
    3. Sleep disturbances (insomnia and disturbed sleep)
    4. Fatigue, tiredness, and low energy levels
    5. Loss of sexual desire and libido
    6. Joint and muscle pains
    7. Headaches
    8. Genitourinary symptoms (vaginal dryness, irritation, discomfort, burning, itching, dyspareunia. This may also include urinary symptoms such as urinary frequency urgency, dysuria, and recurrent lower urinary tract infections)
- Women experiencing menopausal symptoms should be informed about available resources for guidance and encouraged to seek assistance in managing their symptoms.
- Women aged 45 years and older who seek assistance for managing their menopausal symptoms should be provided with treatment options after receiving information and support. This enables them to make informed decisions about their management choices.
- A holistic and individualized approach should be taken when assessing and advising women experiencing menopausal symptoms. Lifestyle advice and dietary modifications, such as weight optimization, smoking cessation, exercise, a healthy diet, and reduced alcohol consumption, should be emphasized.
- Risk factors for cardiovascular disease, bone health, osteoporosis, cancer risk reduction, and management options (including HRT or non-hormonal and alternative therapies) should all be addressed.
- Women interested in HRT should be offered treatment (unless contraindicated) after receiving counseling on the benefits and risks.
- Women should be provided with comprehensive information and ample time to make an informed decision about HRT.

- HRT has consistently demonstrated improvements in menopausal symptoms and overall quality of life and is the most effective treatment for most women.
- Decisions regarding HRT, including dosage, regimen, and duration, should be tailored to each patient after discussing benefits and risks.
- Transdermal estradiol administration is unlikely to increase the risk of venous thrombosis or stroke and may have a lower risk compared to oral administration, making it the preferred route for estradiol administration in women with related risk factors.
- Alternative treatments and non-hormonal options should be explored for women who cannot or choose not to take HRT.
- Women experiencing genitourinary symptoms of menopause should be offered vaginal estrogen treatment. This treatment can be continued on a long-term basis as needed to provide relief from these symptoms.
- Topical vaginal estrogen treatment is effective in alleviating symptoms associated with vaginal atrophy, such as vaginal dryness and superficial dyspareunia.
- Low-dose vaginal estrogen preparations can be used by symptomatic women for as long as needed, and all topical estrogen preparations have demonstrated effectiveness.
- There is no requirement to combine vaginal estrogen with systemic progestogen treatment for endometrial protection, as low-dose vaginal estrogen preparations do not lead to significant systemic absorption or endometrial hyperplasia.
- Women experiencing genitourinary symptoms of menopause have the option to use moisturizers and lubricants either alone or in conjunction with vaginal estrogen treatment to address their symptoms.
- Women undergoing treatment for menopausal symptoms should ideally have a review three months after starting the treatment. Subsequently, they should continue to receive regular reviews, at least annually, to monitor their progress and ensure that the treatment remains appropriate for their needs.
- Treatment duration for menopausal symptoms should be personalized, with no fixed limits on HRT dosage, duration, or age of use. Decisions should align with individual needs and preferences.
- Women continuing HRT use beyond the age of 60 are advised to opt for transdermal estradiol administration.
- Routine cervical and breast screening should be continued following NHS Screening Programme guidelines.

- Women on HRT should undergo regular basic health checks, including annual measurements of weight and blood pressure.
- In menopausal women with low sexual desire for whom HRT with sufficient estrogen intake has not been effective, the consideration of testosterone supplementation is an option.
- Serum androgen level assessment is unlikely to be helpful in diagnosing hormone-dependent low sexual desire due to the poor correlation between circulating androgen levels and clinical symptoms.
- Nevertheless, following best practice recommendations from the Global Consensus Position Statement on the Use of Testosterone Therapy for Women, checking testosterone levels is advised to rule out high baseline levels and prevent excessive replacement.
- When assessing total testosterone levels, it's important to maintain them within the physiological threshold for females.
- Women under the age of 40 who exhibit symptoms indicative of premature ovarian insufficiency (POI) should undergo follicle-stimulating hormone (FSH) level measurement as part of their evaluation.
- Women diagnosed with premature ovarian insufficiency (POI) should be counseled to undergo hormone replacement therapy, and this treatment should be continued until at least the natural age of menopause, unless contraindicated.
- Hormone replacement therapy (HRT) and combined contraceptive pills containing ethinyl estradiol are both viable options for hormone replacement. However, HRT may offer greater benefits for bone health and blood pressure, and it may be associated with lower cardiovascular risk compared to the combined oral contraceptive pill.
- Women experiencing early menopause (aged 40-45 years) should receive information and support similar to women with premature ovarian insufficiency (POI). They should be advised to consider hormone replacement therapy, which should be continued until at least the natural age of menopause.
- Referring to or seeking advice from a specialist menopause service should be considered when specialized input related to menopause is needed.

Section 2.0 Drug Therapy in Menopause

This section comprises three subsections: the first one contains the newly recommended drugs, the second one covers drug modifications, and the third one outlines the drugs that have been withdrawn from the market.

2.1 Additions

After September 2020, there have been no new menopause drugs that have received SFDA approval. Nevertheless, micronized progesterone formulations as gel as well as capsules for oral were registered in the SFDA list and submitted to the CHI for evaluation. Hence, relevant information pertaining to this drug can be found below.

2.1.1 Micronized Progesterone

This section includes pertinent information regarding the use of Micronized progesterone in menopause (Lexicomp 2023)[13]. *Please refer to **section 2.1.2** of CHI Menopause original clinical guidance.*

Table 10. Drug Therapy with Micronized Progesterone (Capsule, Oral Use)

SCIENTIFIC NAME **Micronized Progesterone**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	No
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	N95, N85.0
Drug Class	Progestin
Drug Sub-class	N/A
ATC Code	QG03DA04
Pharmacological Class (ASHP)	Progestin
DRUG INFORMATION	
Dosage Form	Capsule
Route of Administration	Oral use
Dose (Adult) [DDD]*	**Estrogen therapy-associated endometrial hyperplasia, prevention:**

	200 mg once daily for 12 days each month or 100 mg daily continuously **Note:** Indicated in patients with a uterus receiving estrogen therapy (eg, for vasomotor symptoms associated with menopause or secondary amenorrhea). May be administered either cyclically (preferred in late menopausal transition and early postmenopause or functional hypothalamic amenorrhea) or continuously (preferred if >2 to 3 years postmenopause). Discontinue when estrogen therapy is discontinued.
Maximum Daily Dose Adults*	200 mg once daily
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). Use with caution. **Hepatic Impairment:** Use is contraindicated in hepatic impairment or disease.
Prescribing edits*	G, PA, CU
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Indicated in patients with a uterus receiving estrogen therapy (eg, for vasomotor symptoms associated with menopause or secondary amenorrhea)	
G (Gender Edit): Should be used by female patients only.	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): Progestin alone products are essential as alternatives for the relief of postmenopausal symptoms in women who can't tolerate estrogen therapy or as add on to estrogen therapy in menopausal women (postmenopausal or premature ovarian insufficiency) with intact uterus to prevent endometrial hyperplasia and cancer.	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	

PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**<u>Most common:</u>** Abdominal pain, bloating, breast tenderness, mastalgia, urinary tract abnormality, viral infection, depression, dizziness, headache, musculoskeletal pain **<u>Most serious:</u>** Breast cancer, CNS depression, dementia, endometrial cancer, eosinophilic pneumonia, fluid retention, ovarian cancer, retinal thrombosis, toxic shock
Drug Interactions	**<u>Category X</u>**: • Antifungal Agents (Vaginal): This interaction only applies to the vaginal progesterone products and vaginal antifungal products. • Ulipristal **<u>Category D:</u>** • Metyrapone • Sincalide
Special Population	**Older Adult** Refer to adult dosing. **Surgery** Whenever possible, discontinue progestogens in combination with estrogens at least 4 to 6 weeks prior to elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.
Pregnancy	N/A
Lactation	N/A
Contraindications	Hypersensitivity to progesterone or any component of the formulation, including peanuts/peanut oil; undiagnosed abnormal genital

	bleeding; breast cancer (known, suspected, or history of); active deep vein thrombosis, pulmonary embolism, or history of these conditions; active or history of arterial thromboembolic disease (eg, stroke, MI); hepatic impairment or disease; pregnancy.
Monitoring Requirements	Prior to combination hormonal therapy, baseline risk for breast cancer and CVD. During therapy, age appropriate breast and pelvic exams; blood pressure; unscheduled bleeding lasting >6 months for endometrial pathology (sooner in patients who are obese, diabetic, or have a history of endometrial cancer); serum triglycerides (2 weeks after starting therapy in patients with baseline level >200 mg/dL); TSH (6 to 12 weeks after starting oral therapy in patients taking thyroid replacement); efficacy beginning 1 to 3 months after starting therapy, then every 6 to 12 months as appropriate. Duration of treatment should be evaluated at least annually
Precautions	• Cardiovascular disease: Do not use progestogen plus estrogen for the prevention of cardiovascular disease. In the Women's Health Initiative studies, an increased risk of deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarction was observed in patients taking conjugated estrogens combined with medroxyprogesterone. Additional risk factors include diabetes mellitus, hypercholesterolemia, hypertension, systemic lupus erythematosus, obesity, tobacco use, and/or history of venous thromboembolism (VTE).

	Manage risk factors appropriately; discontinue immediately if adverse cardiovascular events occur or are suspected. • Depression: Use with caution in patients with a history of depression; discontinue if serious depression recurs. • Diabetes: May impair glucose tolerance; use caution in patients with diabetes. Prior to therapy, consider age, cardiovascular and metabolic risk factors in patients previously diagnosed with diabetes. • Risks vs benefits: When used for the relief of menopausal symptoms, the benefit-risk of hormone therapy is most favorable if started in patients who have no contraindications to therapy, are <60 years of age, within 10 years of menopause onset, have a favorable lipid profile, and do not have the factor V Leiden genotype or metabolic syndrome. Consider cardiovascular disease risk factors when evaluating therapy and route of administration. Use at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual patient. Reevaluate patients as clinically appropriate to determine if treatment is still necessary. Available data related to treatment risks are from WHI studies, which evaluated oral conjugated estrogens with medroxyprogesterone relative to placebo in patients who are postmenopausal. Other combinations and dosage forms of estrogens and progestogens were

	not studied; assume outcomes to be similar for other doses and other dosage forms of estrogens and progestogens until comparable data becomes available.
Black Box Warning	**Cardiovascular disorders (capsule):** Estrogens plus progestin therapy should not be used for the prevention of cardiovascular disease. **Probable dementia (capsule):** Estrogens plus progestin therapy should not be used for the prevention of dementia. **Breast cancer (capsule):** The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. **Risks versus benefits (capsule):** In the absence of comparable data, assume these risks to be similar for other doses of conjugated estrogens and medroxyprogesterone and other combinations and dosage forms of estrogens and progestins. Prescribe progestins with estrogens at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.
REMS	N/A

Table 11. Drug Therapy with Micronized Progesterone (Vaginal Gel)

SCIENTIFIC NAME Micronized Progesterone	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	No
MHRA	Yes

PMDA	Yes
Indication (ICD-10)	N95, N85.0
Drug Class	Progestin
Drug Sub-class	N/A
ATC Code	QG03DA04
Pharmacological Class (ASHP)	Progestin
DRUG INFORMATION	
Dosage Form	Vaginal gel
Route of Administration	Vaginal use
Dose (Adult) [DDD]*	**Estrogen therapy-associated endometrial hyperplasia, prevention:** 45 mg (4% gel) every other day for up to a total of 6 doses; if response is inadequate, may increase to 90 mg (8% gel) at same schedule. **Note:** Indicated in patients with a uterus receiving estrogen therapy (eg, for vasomotor symptoms associated with menopause or secondary amenorrhea). May be administered either cyclically (preferred in late menopausal transition and early postmenopause or functional hypothalamic amenorrhea) or continuously (preferred if >2 to 3 years postmenopause) (Ref). Discontinue when estrogen therapy is discontinued. **Note:** Dosing is based on manufacturer's labeling; however, intravaginal gel route of administration is considered nonpreferred to oral and is infrequently used due to limited data.
Maximum Daily Dose Adults*	90 mg (8% gel) every other day for up to a total of 6 doses
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** There are no dosage adjustments provided in the manufacturer's labeling. **Hepatic Impairment:**

	Use is contraindicated in hepatic impairment or disease.
Prescribing edits*	G, PA, CU
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Indicated in patients with a uterus receiving estrogen therapy (eg, for vasomotor symptoms associated with menopause or secondary amenorrhea)	
G (Gender Edit): Should be used by female patients only.	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): Progestin alone products are essential as alternatives for the relief of postmenopausal symptoms in women who can't tolerate estrogen therapy or as add on to estrogen therapy in menopausal women (postmenopausal or premature ovarian insuffiency) with intact uterus to prevent endometrial hyperplasia and cancer.	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Abdominal pain, constipation, nausea, breast hypertrophy, mastalgia, nocturia, perineal pain, depression, drowsiness, headache, nervousness, muscle cramps **Most serious:** Breast cancer, CNS depression, dementia, endometrial cancer, eosinophilic pneumonia, fluid retention, ovarian cancer, retinal thrombosis, toxic shock
Drug Interactions	**Category X**: • Antifungal Agents (Vaginal) • Ulipristal **Category D:** • Metyrapone • Sincalide
Special Population	**Older Adult** Refer to adult dosing. **Surgery**

	Whenever possible, discontinue progestogens in combination with estrogens at least 4 to 6 weeks prior to elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.
Pregnancy	N/A
Lactation	N/A
Contraindications	Known sensitivity to Crinone (progesterone or any of the other ingredients), undiagnosed vaginal bleeding, liver dysfunction or disease, Known or suspected malignancy of the breast or genital organs, missed abortion, or active thrombophlebitis or thromboembolic disorders, or a history of hormone-associated thrombophlebitis or thromboembolic disorders
Monitoring Requirements	Monitor serum progesterone levels and adverse effects such as local irritation, allergic reactions, vaginal bleeding, or other unexpected symptoms.
Precautions	• Thrombotic disorders: The physician should be alert to the early manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorder, pulmonary embolism, and retinal thrombosis). Should any of these symptoms occur or be suspected, the drug should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation. • Fluid retention: Because progestogens may cause some degree of fluid retention, conditions that might be influenced by this factor (e.g, epilepsy, migraine,

	asthma, cardiac or renal dysfunction) require careful observation. • Depression: Patients who have a history of depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. • A decrease in glucose tolerance: A decrease in glucose tolerance has been observed in a small percentage of patients on estrogen-progestin combination drugs. The mechanism of this decrease is not known. For this reason, diabetic patients should be carefully observed while receiving progestin therapy.
Black Box Warning	N/A
REMS	N/A

Health Technology Assessment (HTA) – Micronized Progesterone (Oral Use)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of Micronized progesterone (capsules for oral use) for the prevention of estrogen therapy-associated endometrial hyperplasia.**

Health Technology Assessment (HTA) – Micronized Progesterone (Vaginal Gel)

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of Micronized progesterone (capsules for oral use) for the prevention of estrogen therapy-associated endometrial hyperplasia.**

2.2 Modifications

No modifications have been made since September 2020.

2.3 Delisting

The medications below are no longer SFDA registered (SFDA Drug List, July 2023), therefore, it is advisable to delist the following drugs from CHI formulary. *Please refer to* ***Drugs in the disease - section 2*** *of CHI Menopause original clinical guidance*.

- ETHINYLESTRADIOL, NORGESTIMATE

2.4 Other Drugs

Fezolinetant (Veozah™), an oral neurokinin 3 receptor antagonist, was approved by FDA on May 12, 2023, and accepted for regulatory review by EMA in September 2022 for the treatment of moderate to severe vasomotor symptoms, or hot flashes, caused by menopause. Approval was based on the SKYIGHT 1 trial, a phase 3 randomized controlled study, where women aged 40–65 years with an average of seven or more moderate-to-severe hot flashes per day were randomly assigned (1:1:1) to once-daily exact-matched placebo, fezolinetant 30 mg, or fezolinetant 45 mg. Compared with placebo, fezolinetant 30 mg and 45 mg significantly reduced the severity of vasomotor symptoms at week 4 (–0·15 [0·06; p=0·012], –0·19 [0·06; p=0·002]) and week 12 (–0·24 [0·08; p=0·002], –0·20 [0·08; p=0·007]). Improvements in frequency and severity of vasomotor symptoms were observed after 1 week and maintained over 52 weeks[14].

Section 3.0 Key Recommendations Synthesis

- The main objective in therapy should be to use the appropriate and, when possible, the lowest effective dosage of systemic estrogen therapy (ET) that suits the treatment goals, offering advantages while minimizing risks for each individual patient. (Level III)[6]
- The FDA has approved hormone therapy for four distinct purposes: easing moderate to severe vasomotor symptoms (VMS), preventing osteoporosis in postmenopausal women, treating hypoestrogenism caused by hypogonadism, bilateral oophorectomy (BO), or premature ovarian insufficiency (POI), and managing moderate to severe vulvovaginal symptoms. In situations where systemic estrogen therapy is not indicated, FDA guidelines propose the utilization of low-dose topical vaginal estrogen therapy to address genitourinary symptoms related to menopause. (Level I)[6]
- It is crucial to carefully choose the right formulation, dosage, and method of administering progestogen to counter the proliferative impact of systemic estrogen on the endometrium. (Level I)[6]
- Testosterone therapy, when given at doses comparable to natural levels found in premenopausal women, has a favorable effect on sexual function. It results in an increase in satisfying sexual experiences beyond the effects seen with placebo/comparator therapy. Moreover, it enhances different aspects of sexual function, including desire, arousal, orgasmic function, pleasure, and sexual responsiveness, while reducing sexual concerns, including distress. (Level I, Grade A)[7]
- Administering systemic testosterone therapy to postmenopausal women at doses comparable to physiological levels in premenopausal women may result in mild increases in acne and body/facial hair growth in some individuals. However, there is no evidence of associations with alopecia (hair loss), clitoromegaly (enlargement of the clitoris), or voice changes. (Level I, Grade A)[7]
- In postmenopausal women with normal adrenal function, systemic dehydroepiandrosterone (DHEA) does not significantly improve libido or sexual function and is not recommended for those with HSDD (Hypoactive Sexual Desire Disorder). (Level IA, Grade A)[7]
- Hormone therapy remains the preferred method for relieving vasomotor symptoms (VMS)[6].
- Women who do not have a uterus can opt for estrogen-alone therapy. (Level I)[6]

- Women with a uterus have the choice of either estrogen-progestin therapy (EPT) or tissue-selective estrogen complex (TSEC) to safeguard against endometrial neoplasia. (Level I)[6]
- SSRIs, SNRIs, or clonidine should not be routinely recommended as the initial treatment for vasomotor symptoms alone[8].
- Non-hormonal prescription therapies, such as specific antidepressant medications, gabapentin, and clonidine, may provide some relief from hot flashes, but they come with their own set of side effects. These alternatives can be taken into consideration when hormone therapy is not recommended or preferred. (I-B)[5]
- CBT can be used to (CBT) to reduce feelings of low mood or anxiety that emerge due to menopause[8].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Menopause report** and aims to provide recommendations to aid in the management of Menopause. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Hypothyroidism. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Menopause Scope

2020	Changes	2023	Rationale
Section 1.0 Menopause Clinical Guidelines			
Menopause: diagnosis and management NICE guideline Published: 12 November 2015 updated 5 December 2019	N/A		
SOGC Clinical Practice Guideline Endometriosis: Managing Menopause 2014	N/A		
Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline 2015	N/A		
	Missing	Global Consensus Position Statement on the Use of Testosterone	• Testosterone can exert its effects in two ways: either by directly interacting with the androgen receptor through non-genomic androgenic action, or by

		Therapy for Women (2019)[7]	converting into the stronger androgen dihydrotestosterone, and/or being transformed into estradiol and its metabolites through aromatization. • Testosterone levels decrease throughout the reproductive years (Level IIB). • In women, testosterone levels seem to remain stable after the age of 65, but it is not yet clear if this has any advantageous effects (Level IIB). • Liquid/gas chromatography and tandem mass spectrometry assays provide highly accurate and reproducible measurements of total testosterone (Grade B). • The primary emphasis in current research on testosterone physiology and clinical effects should be on measuring total testosterone as the primary biomarker, rather than "free" testosterone, since there is a lack of evidence supporting that "free" testosterone is the biologically active fraction of testosterone (Expert Opinion). • Hypoactive sexual desire disorder/dysfunction (HSDD) and female sexual arousal disorder (FSAD) are separate conditions that need to be categorized independently when studying the effects of androgens on their clinical manifestations and

			treatment outcomes (Grade B). • While HSDD and FSAD may share some similarities, they have different causes, risk factors, clinical characteristics, and responses to psychological and biological treatments (Grade B). **Recommendations regarding testosterone treatment of naturally or surgically postmenopausal women with HSDD, with/or without concurrent estrogen therapy** • Testosterone therapy, when administered at doses similar to physiological levels in premenopausal women, has a positive impact on sexual function. It leads to an increase in satisfying sexual events, exceeding the effects observed with placebo/comparator therapy. Additionally, it improves various aspects of sexual function, such as desire, arousal, orgasmic function, pleasure, and sexual responsiveness, while reducing sexual concerns, including sexual distress (Level I, Grade A). • It is important to note that the studies assessing sexual function primarily included women diagnosed with HSDD or generalized FSD. Therefore, these recommendations may not apply to other subtypes of FSD or women without

			sexual dysfunction (Expert Opinion). **Recommendations regarding the effects of testosterone on wellbeing, mood, and cognition in postmenopausal women** • There is not enough evidence to back the use of testosterone for boosting cognitive performance or delaying cognitive decline in postmenopausal women (Insufficient). • Based on the currently available data, testosterone therapy does not appear to have any impact on general wellbeing (Level I, Grade A). • Testosterone might have a positive effect on wellbeing in premenopausal women, but the existing data are inconclusive (Level 1, Grade B). • The available data do not demonstrate any effect of testosterone on alleviating depressed mood (Level I, Grade B). **Recommendations regarding the musculoskeletal effects of testosterone** • Based on the evidence available, there is no support for the idea that testosterone treatment has an effect on bone mineral density at the spine, total hip, or femoral neck after 12 months (Level I, Grade A). • Studies have not shown any statistically significant impact of testosterone administered in

			physiological doses on lean body mass, total body fat, or muscle strength (Level I, Grade A). • Expert opinion suggests that clinical trials are necessary to assess the influence of testosterone treatment on musculoskeletal tissues. **Recommendations regarding possible androgenic side effects of testosterone therapy** • Systemic testosterone therapy for postmenopausal women, when administered at doses similar to physiological levels found in premenopausal women, may lead to slight increases in acne and body/facial hair growth in certain individuals. However, it is not associated with alopecia (hair loss), clitoromegaly (enlargement of the clitoris), or voice changes (Level I, Grade A). **Recommendations regarding testosterone therapy and cardiovascular health** • Taking testosterone orally is linked to unfavorable lipid profiles, causing negative impacts on high-density lipoprotein-cholesterol and low-density lipoprotein-cholesterol levels. As a result, oral testosterone therapy is not recommended (Level I, Grade A).

			• (b) Research on nonoral testosterone therapies (such as percutaneous and injectable methods) at doses similar to physiological levels found in premenopausal women has not shown any statistically significant adverse effects on lipid profiles in the short term (Level I, Grade A). • (c) Testosterone therapy has not been associated with increases in blood pressure, blood glucose, or HbA1c levels (Level I, Grade A). • (d) There has been a non-significant trend indicating a potential increased risk of deep venous thrombosis with testosterone therapy. However, the role of concurrent estrogen therapy in this potential venous thrombosis risk needs further investigation (Level I, Grade A). **Recommendations regarding testosterone therapy and breast health** • Testosterone therapy does not lead to an increase in mammographic breast density (Level I, Grade A). • The data currently available indicate that short-term transdermal testosterone therapy does not have an effect on the risk of developing breast cancer (Level I, Grade A).

			Recommendations regarding current testosterone therapy and postmenopausal women • The only well-supported reason for using testosterone in women is for the treatment of postmenopausal women diagnosed with HSDD following a comprehensive biopsychosocial evaluation (Level I, Grade A). • There is a recognized gap in the availability and approval of testosterone treatments tailored specifically for women, with the goal of achieving testosterone levels similar to those found in premenopausal women (Expert Opinion). • If a suitable approved testosterone product specifically designed for females is not accessible, prescribing an approved male formulation off-label can be considered reasonable, if hormone concentrations are kept within the physiological range for females (Expert Opinion). • It is not recommended to use any form of testosterone preparation that leads to higher-than-physiological levels of testosterone, such as pellets and injections (Expert Opinion). • Before starting a trial of testosterone therapy for HSDD, a baseline total testosterone level should be measured, and a follow-up test should be conducted 3

			to 6 weeks after initiating treatment (Level IIA, Grade C). • Patients undergoing testosterone therapy should be regularly monitored for their clinical response to the treatment, and their serum total testosterone level should be checked every 6 months to detect any signs of androgen excess and potential overuse (Expert Opinion). • If no improvement is observed within 6 months of treatment, it is recommended to discontinue the therapy (Level IB, Grade C). **Recommendations regarding other androgenic preparations** • For postmenopausal women with normal adrenal function, systemic dehydroepiandrosterone does not show substantial improvement in libido or sexual function and is not recommended for those with HSDD (18) (Level IA, Grade A). • (b) The effectiveness of vaginal dehydroepiandrosterone for the treatment of HSDD has not been studied in the absence of vulvovaginal atrophy, and therefore, it cannot be recommended for such use (Expert Opinion).

	Missing	The 2022 hormone therapy position statement of The North American Menopause Society[6]	• The primary therapeutic goal should be to use the appropriate and often the lowest effective dose of systemic estrogen therapy (ET) that aligns with treatment objectives, providing benefits while minimizing risks for each individual woman (Level III). • Various formulations, doses, and administration routes of hormone therapy have similarly high efficacy in relieving vasomotor symptoms (VMS) (Level I). • Decisions regarding the formulation, dose, and administration route of hormone therapy should be tailored individually for each woman and should be periodically reevaluated (Level III). • Different hormone therapy doses, formulations, and administration routes may have distinct effects on target organs, offering potential options to reduce risks (Level II). • To counteract the proliferative effects of systemic estrogen on the endometrium, selecting the appropriate formulation, dose, and administration route of progestogen is essential (Level I). • Hormone therapy has received FDA approval for four specific indications: alleviation of moderate to severe vasomotor symptoms (VMS),

			prevention of osteoporosis in postmenopausal women, treatment of hypoestrogenism resulting from hypogonadism, bilateral oophorectomy (BO), or premature ovarian insufficiency (POI), and management of moderate to severe vulvovaginal symptoms. In cases where there are no indications for systemic estrogen therapy, FDA guidance suggests the use of low-dose topical vaginal estrogen therapy for the treatment of genitourinary symptoms associated with menopause (Level I). • Compounded bioidentical hormone therapy (estradiol, estrone, and micronized progesterone (MP)), raises safety issues due to limited government regulation and monitoring, the risk of overdosing or underdosing, the possibility of impurities and lack of sterility, inadequate scientific evidence regarding efficacy and safety, and the absence of a label clearly indicating potential risks (Level I). • Compounded bioidentical hormones may be considered in specific situations, such as when there are allergies to ingredients present in government-approved formulations or when required dosages are not available in government-approved products (Level III).

			Vasomotor symptoms • Hormone therapy remains the preferred method for relieving vasomotor symptoms (VMS). • For women without a uterus, estrogen-alone therapy can be used. (Level I) • For women with a uterus, either estrogen-progestin therapy (EPT) or tissue-selective estrogen complex (TSEC) can be used to protect against endometrial neoplasia. (Level I) • When deciding on the formulation, administration route, and dosage of hormone therapy for menopause symptom management, shared decision-making should be employed, considering symptom relief, adverse effects, and patient preferences. (Level III) • The necessity of continued hormone therapy should be periodically assessed based on a woman's menopause symptoms, overall health, underlying medical conditions, risks, treatment goals, and personal preferences. (Level III) • Taking 300 mg of micronized progesterone nightly has shown significant reduction in vasomotor symptoms (hot flashes and night sweats) and improved sleep when compared to placebo. Synthetic progestins have also demonstrated some benefit for VMS in certain

			studies. Long-term study results are lacking, and using progestogens without estrogen for these indications is considered off-label. (Level II) **Sleep disturbances** • Hormone therapy enhances sleep in women experiencing bothersome nighttime vasomotor symptoms (VMS) by reducing instances of nighttime awakenings. Additionally, estrogen may have some impact on sleep, unrelated to the effects of VMS. (Level II) **Genitourinary symptoms** • Low-dose vaginal estrogen therapy (ET) preparations are effective and generally safe for treating genitourinary symptoms of genitourinary syndrome of menopause (GSM). They have minimal systemic absorption and are preferred over systemic therapies when ET is solely used for managing genitourinary symptoms. (Level I) • For women with breast cancer, prescribing low-dose vaginal estrogen therapy should be done in consultation with their oncologists. (Level III) • When using low-dose vaginal estrogen, progestogen therapy is not required, although randomized controlled trial

			(RCT) data are lacking beyond a 1-year duration. (Level II) • FDA-approved nonestrogen prescription therapies that improve vulvovaginal atrophy (VVA) in postmenopausal women include ospemifene and intravaginal dehydroepiandrosterone (DHEA). (Level I) **Urinary tract symptoms (including pelvic floor disorders)** • Systemic hormone therapy does not lead to improvements in urinary incontinence and might even increase the incidence of stress urinary incontinence. (Level I) • Low-dose vaginal estrogen therapy (ET) may offer advantages for urinary symptoms, including preventing recurrent urinary tract infections (UTIs), managing overactive bladder, and urge incontinence. (Level II) • Hormone therapy has not received FDA approval for any urinary health indication. (Level I) **Sexual function** • Both systemic hormone therapy and low-dose vaginal estrogen therapy (ET) have the effect of increasing lubrication, blood flow, and sensation in vaginal tissues. (Level I)

			• Systemic hormone therapy, in general, does not independently improve sexual function, sexual interest, arousal, or orgasmic response, apart from its impact on genitourinary syndrome of menopause (GSM). (Level I) • For women experiencing menopause symptoms and concerned about sexual function or libido, transdermal estrogen therapy may be preferable over oral estrogen therapy due to its minimal effect on sex hormone-binding globulin and free testosterone levels. (Level II) • Low-dose vaginal estrogen therapy improves sexual function in postmenopausal women with GSM. (Level I) • FDA-approved nonestrogen alternatives for dyspareunia include ospemifene and intravaginal dehydroepiandrosterone (DHEA). (Level I) **Primary Ovarian Insufficiency** • Women with premature ovarian insufficiency (POI) or experiencing premature or early menopause may face elevated risks of various health conditions, including fractures, cardiovascular disease (CVD), heart failure, diabetes mellitus (DM), overall mortality, persistent vasomotor symptoms (VMS), fertility loss, bone loss, genitourinary symptoms, sexual

			dysfunction, cognitive and mood changes, increased risk of dementia, open-angle glaucoma, depression, and reduced quality of life. (Level II) • If there are no contraindications, hormone therapy is suggested to be used until at least the average age of menopause, which is around 52 years old. In healthy younger women, oral contraceptives are also an alternative for treatment. (Level II) Young women facing the risk of premature ovarian insufficiency (POI) should consider fertility preservation options and counseling. (Level III) • For premenopausal women at average risk for ovarian cancer who require hysterectomy for non-cancerous reasons, it is advised to retain the ovaries (ovarian conservation). (Level II) **Skin, hair, and special senses** • Estrogen therapy administered during menopause seems to have positive effects on skin thickness, elasticity, and collagen. (Level II) • Hormone therapy seems to lower the risk of neovascular and soft drusen age-related macular degeneration, but it does not affect early or late-stage macular degeneration. (Level II)

			• Estrogen therapy appears to decrease intraocular pressure and potentially reduce the risk of open-angle glaucoma in Black women. (Level II) **Osteoporosis** • Hormone therapy is effective in preventing bone loss in healthy postmenopausal women, and its impact on bone density is dose-related. (Level I) • In healthy postmenopausal women, hormone therapy reduces the risk of fractures. (Level I) • Rapid bone loss occurs when hormone therapy is discontinued, but the Women's Health Initiative (WHI) study did not observe an excess of fractures after discontinuation. (Level I) • Hormone therapy is FDA-approved for preventing bone loss but not for the treatment of osteoporosis. (Level I) • In women younger than 60 years of age or within 10 years of menopause onset, systemic hormone therapy is appropriate to safeguard against bone loss if there are no contraindications. (Level I) • For women with premature menopause and no prior fragility fracture or osteoporosis, the best approach is to use hormone therapy or oral contraceptives to prevent

			bone density loss and reduce fracture risk until the average age of menopause, at which point treatment may be reevaluated. Other bone-specific treatments should be considered only if contraindicated. (Level II) **Sarcopenia** Preclinical investigations indicate a potential advantage of estrogen therapy (ET) when used in conjunction with exercise to prevent muscle mass loss, strength decline, and performance deterioration. However, such outcomes have not been demonstrated in clinical trials. (Level II) **Gallbladder and Liver** • The use of estrogen therapy (ET) and estrogen-progestin therapy (EPT) is associated with an elevated risk of gallstones, cholecystitis, and cholecystectomy. (Level I) **Metabolic syndrome and diabetes** • Hormone therapy leads to a substantial decrease in the incidence of new-onset type 2 diabetes mellitus (DM), but it is not officially approved by the government for this purpose. (Level I) • For otherwise healthy women with preexisting type 2 DM, hormone therapy is not

			contraindicated and may be beneficial in terms of glycemic control when used to manage menopause symptoms. (Level II) • While hormone therapy might assist in mitigating abdominal adipose accumulation and weight gain related to menopause transition, the effect is modest. (Level II) **Cognition** • Until more conclusive evidence is available, hormone therapy is not advised at any age as a preventive or treatment measure for cognitive decline or dementia. (Level I) • Estrogen therapy might offer cognitive advantages if started promptly after hysterectomy with bilateral oophorectomy. However, during the early natural postmenopause period, hormone therapy appears to have neutral effects on cognitive function. (Level II) **Depression** • There is evidence suggesting that estrogen therapy (ET) exhibits antidepressant effects of comparable magnitude to those observed with antidepressant agents when given to perimenopausal women experiencing depression, with or without concurrent

			vasomotor symptoms (VMS). (Level II) • Estrogen therapy (ET) is not effective in treating depressive disorders in postmenopausal women. However, there is evidence suggesting a potential window of opportunity for using ET effectively to manage depressive disorders during the perimenopause period. (Level II) • Some evidence indicates that ET can improve mood and enhance overall well-being in nondepressed perimenopausal women. (Level II) • The use of transdermal estradiol with intermittent progestogen may prevent the onset of depressive symptoms in euthymic perimenopausal women. However, there is insufficient evidence to recommend estrogen-based therapies for preventing depression in asymptomatic perimenopausal or postmenopausal women, and the risks and benefits must be carefully evaluated. (Level II) **Cardiovascular disease and all-cause mortality** • For healthy symptomatic women below 60 years of age or within 10 years of menopause onset, the beneficial effects of hormone therapy on coronary heart disease

			(CHD) and all-cause mortality should be weighed against potential rare increases in risks of breast cancer, venous thromboembolism (VTE), and stroke. (Level I) • Hormone therapy is not approved by the government for primary or secondary cardioprotection. (Level I) • When considering the initiation of hormone therapy, personal and familial risks of cardiovascular disease (CVD), stroke, VTE, and breast cancer should be considered. (Level III) • The effects of hormone therapy on CHD may vary based on when it is started in relation to a woman's age or time since menopause onset. (Level I) • In randomized, controlled trials, initiating hormone therapy in recently postmenopausal women either reduced or had no effect on the progression of subclinical atherosclerosis and coronary artery calcification. (Level I) • Observational data and meta-analyses demonstrate a reduced risk of CHD in women who start hormone therapy before the age of 60 years or within 10 years of menopause onset. However, meta-analyses show no significant effect of hormone therapy on CHD after excluding open-label trials. (Level II)

			• Women who begin hormone therapy after the age of 60 years or more than 10 or 20 years from menopause onset face higher absolute risks of CHD, VTE, and stroke compared to women who start hormone therapy during early menopause. (Level I) **Breast Cancer** • Women should receive counseling regarding the risk of breast cancer associated with hormone therapy. It is important to put the data into perspective, as the risk is similar to that of modifiable risk factors like consuming two alcoholic beverages daily, being obese, and having low physical activity. (Level III) • The impact of hormone therapy on breast cancer risk may vary depending on factors such as the type of hormone therapy, duration of use, regimen, prior exposure to hormones, and individual characteristics. (Level II) • Different hormone therapy regimens might be linked to increased breast density, potentially leading to difficulties in mammographic interpretation. This could result in the need for more mammograms or breast biopsies and may lead to a potential delay in breast cancer diagnosis. (Level II)

			• The majority of available data do not indicate an additional effect of hormone therapy use on breast cancer incidence when considering factors such as age, family history of breast cancer, genetic risk of breast cancer, benign breast disease, and personal breast cancer risk factors. (Level II) • There is insufficient data to assess the risk of breast cancer with newer therapies, like tissue-selective estrogen complexes (TSECs), including BZA plus CEE. (Level II) • Observational evidence suggests that hormone therapy use does not further increase breast cancer risk in women at high risk due to a family history of breast cancer or after undergoing bilateral salpingo-oophorectomy (BSO) for BRCA1 or BRCA2 genetic variants. (Level II) • For breast cancer survivors, systemic hormone therapy is generally not recommended. However, it may be considered for women with severe vasomotor symptoms (VMS) that are unresponsive to nonhormone options, in consultation with their oncologists and through shared decision-making. (Level III) • For breast cancer survivors experiencing genitourinary symptoms of menopause (GSM), low-dose vaginal

			estrogen therapy (ET) or dehydroepiandrosterone (DHEA) may be considered, with consultation with their oncologists, if bothersome symptoms persist after trying nonhormone therapy. Concerns are heightened when considering low-dose vaginal ET for women on aromatase inhibitors (AIs). (Level III) • Regular breast cancer surveillance is recommended for all postmenopausal women according to current breast cancer screening guidelines, including those using hormone therapy. (Level I) **Endometrial cancer** • Unopposed systemic estrogen therapy (ET) in postmenopausal women with an intact uterus increases the risk of endometrial cancer, making it crucial to use adequate progestogen alongside it. (Level I) • Low-dose vaginal estrogen therapy (ET) does not seem to elevate the risk of endometrial cancer, although trials with endometrial biopsy endpoints have been limited to a duration of 1 year. (Level II) • Hormone therapy may be considered as an option for treating bothersome menopause symptoms in women who have surgically

			treated, early stage, low-grade endometrial cancer. This decision should be made in consultation with the woman's oncologist if nonhormone therapies have been ineffective. (Level II) • Systemic hormone therapy is not recommended for use in cases of high-grade, advanced-stage endometrial cancers or with endometrial stromal sarcomas or leiomyosarcomas. (Level II) **Ovarian Cancer** • Taking oral contraceptives is linked to a substantial decrease in the risk of ovarian cancer. (Level I) • In observational studies, current and recent use of hormone therapy is associated with a slight but statistically significant risk of ovarian cancer, primarily for the serous type. However, women enrolled in the WHI who were randomized to estrogen-progestin therapy (EPT) did not experience an increased risk of ovarian cancer. (Level II) • In women with a history of ovarian cancer, the benefits of hormone therapy use generally outweigh the risks, particularly when dealing with bothersome vasomotor symptoms or early menopause. Nonetheless, hormone therapy is not

			recommended for women with hormone-dependent ovarian cancers, including granulosa-cell tumors and low-grade serous carcinoma. (Level II) **Colorectal cancer** • Observational studies indicate a lower occurrence of colorectal cancer in women currently using hormone therapy, leading to reduced mortality rates. (Level II) • In the Women's Health Initiative (WHI) study, estrogen-progestin therapy (EPT) was found to reduce the risk of colorectal cancer, but not estrogen therapy (ET) alone. However, cancers detected in EPT users were diagnosed at a more advanced stage. There was no difference in colorectal cancer mortality with either EPT or ET. (Level I)
	Missing Guideline	**Menopause and risk of thromboembolic events. Postmenopausal women management: CNGOF and GEMVi clinical practice guidelines (2021)**[9]	• Oral estrogens (ECE and estradiol) increase the risk of VTE in the general population by 1.7 compared to placebo (LE1). The risk seems greater with ECE compared to 17-β-estradiol (LE2). • Dermal estradiol does not seem to increase the risk of VTE in the general population (LE2). • The risk of VTE seems to be modulated according to the type of combined progestogen of the

			THM. The risk of VTE associated with the use of a THM composed of estradiol by the dermal route seems neutral in users of micronized progesterone and pregnane derivatives and increased in users of norpregnane derivatives in the general population (LE2). • In women with a personal history of VTE (DVT or PE), HRT composed of oral estrogen therapy increases the risk of recurrence of VTE (LE1). HRT with cutaneous estrogen therapy seems neutral with respect to the risk of recurrence of VTE (LE3). • In women with a factor V Leiden mutation or a prothrombin G20210A mutation, HRT compounded with oral estrogen therapy increases the risk of VTE (LE1). THM composed of cutaneous estrogen therapy seems neutral with respect to the risk of VTE (LE3) • The use of a THM composed of oral estrogen therapy in obese women increases the risk of VTE (LE1). In dermal estradiol users, there does not seem to be any increased risk of VTE regardless of the BMI (LE2). • The use of vaginal estradiol as part of the treatment of vulvovaginal atrophy does not seem to increase the risk of VTE (LE3).

	Missing	Japan Society of Obstetrics and Gynecology and Japan Society for Menopause and Women's Health 2017 guidelines for hormone replacement therapy[10]	**Characteristics of HRT and General Precautions for Use** • When used appropriately, hormone replacement therapy (HRT) can be advantageous for enhancing or sustaining the quality of life in postmenopausal women. However, there might be instances where it could lead to adverse effects. It is essential to thoroughly evaluate the benefits and risks associated with HRT before considering its use. • Progestogen is administered to prevent endometrial hyperplasia and the elevated risk of endometrial cancer that may occur during systemic estrogen therapy. As a result, it is not necessary for women without a uterus or those receiving lower doses of vaginal estrogen. • To mitigate the heightened risk of endometrial cancer, the combined use of estrogen and progestogen is essential for women with a uterus. **Expected effects of HRT** • Both oral and transdermal estrogen are effective in alleviating hot flashes. • Conjugated equine estrogen (CEE) offers relief from a range of menopausal symptoms, including night sweats, sexual dysfunction, insomnia, vaginal dryness, memory loss, frequent urination, and psychological

			symptoms, in addition to hot flashes. • When combined with medroxyprogesterone acetate (MPA), CEE enhances health-related quality of life. • Estradiol (E2) is effective in improving sleep disorders, joint pain, and limb pain, along with alleviating hot flashes. • Hormone replacement therapy (HRT) has the potential to prevent or alleviate joint pain. (Level of Recommendation: 2, Level of Evidence (+ + − −)) • HRT is considered effective for insomnia. (Level of Recommendation: 2, Level of Evidence (+ + + −)) • When organic diseases have been ruled out, hormone replacement therapy (HRT) has been found to be effective in addressing back pain, which is considered a symptom of menopausal disorder. (Level of Recommendation: 2, Level of Evidence (+ −−−)) • HRT does not directly impact pelvic organ prolapse, but it does improve related lower urinary tract symptoms, vaginal atrophy, and vaginal dryness. (Level of Recommendation: 2, Level of Evidence (+ + − −))

			• HRT improves dyspareunia and vaginal lubrication. (Level of Recommendation: 1, Level of Evidence (+ + + −)) • The topical application of estrogen is beneficial in managing overactive bladder symptoms. (Level of Recommendation: 2, Level of Evidence (+ + + −)) • HRT can be used in smokers, but it is important to note that the beneficial effects may be reduced, and there could be an increase in adverse events. Therefore, it is essential to offer guidance on adopting appropriate lifestyle habits, including smoking cessation, alongside HRT. (Level of Recommendation: 2 Level of Evidence (+ + − −)) • HRT is possible for obese patients, although careful administration or conditional administration is necessary. (Level of Recommendation: 2, Level of Evidence (+ + − −)) • HRT is feasible for women with a history of endometriosis, but careful consideration should be given to the recurrence of clinical symptoms, the worsening or possible malignant transformation of the lesions. (Level of Recommendation: 1, Level of Evidence (+ + − −))

			• HRT is possible for women with controlled high blood pressure. (Level of Recommendation: 2, Level of Evidence (+ + − −)) • HRT is possible for women with diabetes mellitus with satisfactorily controlled blood glucose and no arteriosclerotic disease. (Level of Recommendation: 2, Level of Evidence (+ + − −)) • HRT recommended for women with premature ovarian insufficiency (POI) (Level of Recommendation: 1, Level of Evidence (+ + − −)) • HRT is recommended for cervical cancer survivors. (Level of Recommendation: 1 Level of Evidence (+ + + −)) • HRT is recommended for ovarian cancer survivors. (Level of Recommendation: 1, Level of Evidence (+ + − −)) • HRT is possible for women with BRCA1/2 gene mutation for a short term. (Level of Recommendation: 1, Level of Evidence (+ + + −)) • HRT is recommended for women with no estrogen deficiency symptoms if there is a clear goal(s), with benefits outweighing risks. (Level of Recommendation: 1 Level of Evidence (+ −−−)) • Oral estriol monotherapy can be utilized in women with a uterus, but it is crucial to monitor for endometrial hyperplasia

			and genital bleeding. For long-term administration, it is generally advisable to consider the concurrent use of progestogen. (Level of Recommendation: 1, Level of Evidence (+ + − −)) • Bazedoxifene, when used together with conjugated estrogen, is known to offer endometrial protection, suggesting a potential alternative to progestogens. (Level of Recommendation: 2, Level of Evidence (+ + − −)) • HRT can be considered for initiation in women over the age of 60 if there is a clear medical indication, and if the potential benefits outweigh the associated risks. (Level of Recommendation: 2, Level of Evidence (+ + + −)) • There are no specific age limits or set time periods that restrict the continuation of HRT. (Level of Recommendation: 1, Level of Evidence (+ −−−)
	Missing	Clinical impact of 2020 American Heart Association statement on menopause and cardiovascular disease risk[11]	**Lifestyle interventions** Female patients going through menopause in midlife should receive regular counseling on lifestyle interventions designed to promote ideal cardiovascular health. Following the American Heart Association's Life's Simple 7 components, achieving ideal cardiovascular health involves implementing the following interventions: • Smoking cessation

			• Weight management to achieve an ideal body weight (body mass index < 25 kg/m2) • Optimization of cholesterol levels: total cholesterol < 200 mg/dL, low density lipoprotein cholesterol (LDL-C) < 100 mg/dL, high density lipoprotein cholesterol (HDLC) > 50 mg/dL, triglycerides < 150 mg/dL, non–HDL-C < 130 mg/dL) • Optimization of blood pressure levels (< 120/80 mmHg) • Optimization of fasting blood glucose (goal < 100 mg/dL) • Engaging in at least 150 min/week of moderate-intensity exercise or 75 minutes per week of vigorous exercise (or a combination of both) • A DASH (Dietary Approaches to Stop Hypertension) diet. **Aspirin use** Although not extensively covered in this scientific statement, previous American Heart Association (AHA) guidelines have stated that the use of aspirin for primary prevention of heart attack is not recommended in female

			patients who are under the age of 65 and do not have cardiac risk factors. This recommendation is based on a careful assessment of the potential risks and benefits of aspirin therapy in this specific population. It is essential for healthcare providers to consider individual patient characteristics and risk factors when making decisions about aspirin use for heart attack prevention. **Lipid-lowering interventions** • As mentioned previously, primary approaches for improving lipid levels in middle-aged female patients involve lifestyle adjustments like regular physical activity, achieving and sustaining a healthy body weight, refraining from smoking, and adopting a heart-healthy diet. • The impact of omega-3 and omega-6 fatty acid supplementation or dietary consumption on reducing the risk of coronary heart disease, heart attacks, lowering total cholesterol levels, or decreasing rates of cardiovascular or overall mortality remains unclear in

			midlife women. This uncertainty leaves us uncertain about the potential effects, if any, of omega-3 and omega-6 fatty acids on preventing cardiovascular disease in this population. • For both primary and secondary prevention, women with hypercholesterolemia and/or hypertriglyceridemia may contemplate incorporating omega-3 fatty acids into their diets through fish consumption or by taking capsules, such as eicosapentaenoic acid at a dose of 1800 mg per day. • The use of HMG-CoA reductase inhibitors, commonly known as statins, for reducing the risk of cardiovascular disease in middle-aged women continues to be a subject of debate and controversy. • The scientific statement from the American Heart Association (AHA) highlighted that evidence regarding

			the effectiveness of lipid-lowering medications for both primary and secondary prevention, as well as for enhancing survival in women, remains inconclusive. As of now, non-pharmacological approaches are considered the primary strategies for enhancing lipid profiles. • Moreover, considering that diabetes is a recognized risk factor for cardiovascular disease (CVD), it is essential to acknowledge that some studies have indicated an elevated risk of diabetes in postmenopausal women who use statins. • The most prevalent nonstatin therapies include bile acid sequestrants, cholesterol absorption inhibitors, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. These may be employed either alongside or as alternatives to statins

			for reducing cholesterol levels in specific patients. However, their use for primary cardiovascular disease prevention in both men and women remains uncertain. Consequently, sex-specific trials are needed to ascertain their effectiveness in this regard. **Supplements** • At present, there are no vitamin or antioxidant supplements recommended for either primary or secondary prevention of cardiovascular disease (CVD). **Menopausal hormone therapy** • There is limited data on how menopausal hormone therapy (HT) affects perimenopausal women's cardiometabolic health. • The impact of HT on atherosclerosis and CVD event progression varies based on age and when HT is initiated.

			• Currently, HT and selective estrogen receptor modulators are not recommended for primary or secondary CVD prevention in postmenopausal women. • However, research suggests that early HT initiation in cases of premature or surgical menopause and within ten years of natural menopause may have cardiovascular benefits. • Using HT to counter early estrogen loss is considered standard care, but individualized assessment is crucial.
	Missing	Menopause Practice Standards by British Menopause Society (BMS) Royal College of Obstetricians and Gynaecologists (RCOG) Society for Endocrinology (SfE) Faculty of Sexual and Reproductive Health (FSRH) Faculty of Pharmaceutical Medicine (FPM) Royal Pharmaceutical Society [12](RPS) (2022)	• The diagnosis of perimenopause or menopause in women aged 45 years and over, who are experiencing menopausal symptoms, can typically be established based on their symptoms alone. Confirmatory blood tests (FSH, oestradiol) are generally unnecessary unless there is uncertainty about the diagnosis.

			• Many women may encounter bothersome menopausal symptoms even when they are in the perimenopausal phase, which is the period leading up to menopause characterized by irregular menstrual cycles and possibly menopausal symptoms. It is important to consider this when evaluating women's health. • The most common symptoms experienced during menopause include: 1. Vasomotor symptoms (hot flushes/night sweats). 2. Cognitive symptoms and mood disorders (low mood, labile mood, anxiety, irritability, loss of confidence, low self-esteem, difficulties with short-term concentration and memory ('Brain fog'), and difficulties

			in multi-tasking). 3. Sleep disturbances (insomnia and disturbed sleep) 4. Fatigue, tiredness and low energy levels 5. Loss of sexual desire and libido 6. Joint and muscle pains 7. Headaches 8. Genitourinary symptoms (vaginal dryness, irritation, discomfort, burning, itching, dyspareunia. This may also include urinary symptoms such as urinary frequency urgency, dysuria and recurrent lower urinary tract infections) • Women experiencing menopausal symptoms should be informed about available resources for guidance and encouraged to seek

			assistance in managing their symptoms. • Women aged 45 years and older who seek assistance for managing their menopausal symptoms should be provided with treatment options after receiving information and support. This enables them to make informed decisions about their management choices. • A holistic and individualized approach should be taken when assessing and advising women experiencing menopausal symptoms. Lifestyle advice and dietary modifications, such as weight optimization, smoking cessation, exercise, a healthy diet, and reduced alcohol consumption, should be emphasized. • Risk factors for cardiovascular disease, bone health, osteoporosis, cancer risk reduction, and management

			options (including HRT or non-hormonal and alternative therapies) should all be addressed. • Women interested in HRT should be offered treatment (unless contraindicated) after receiving counseling on the benefits and risks. • Women should be provided with comprehensive information and ample time to make an informed decision about HRT. • HRT has consistently demonstrated improvements in menopausal symptoms and overall quality of life and is the most effective treatment for most women. • Decisions regarding HRT, including dosage, regimen, and duration, should be tailored to each patient after discussing benefits and risks. • Transdermal estradiol administration is unlikely to increase the risk of venous thrombosis or stroke and may have a

			lower risk compared to oral administration, making it the preferred route for estradiol administration in women with related risk factors. • Alternative treatments and non-hormonal options should be explored for women who cannot or choose not to take HRT. • Women experiencing genitourinary symptoms of menopause should be offered vaginal estrogen treatment. This treatment can be continued on a long-term basis as needed to provide relief from these symptoms. • Topical vaginal estrogen treatment is effective in alleviating symptoms associated with vaginal atrophy, such as vaginal dryness and superficial dyspareunia. • Low-dose vaginal estrogen preparations can be used by symptomatic women for as long as needed, and all topical estrogen

			preparations have demonstrated effectiveness. • There is no requirement to combine vaginal estrogen with systemic progestogen treatment for endometrial protection, as low-dose vaginal estrogen preparations do not lead to significant systemic absorption or endometrial hyperplasia. • Women experiencing genitourinary symptoms of menopause have the option to use moisturizers and lubricants either alone or in conjunction with vaginal estrogen treatment to address their symptoms. • Women undergoing treatment for menopausal symptoms should ideally have a review three months after starting the treatment. Subsequently, they should continue to receive regular reviews, at least annually, to monitor

			their progress and ensure that the treatment remains appropriate for their needs. • Treatment duration for menopausal symptoms should be personalized, with no fixed limits on HRT dosage, duration, or age of use. Decisions should align with individual needs and preferences. • Women continuing HRT use beyond the age of 60 are advised to opt for transdermal estradiol administration. • Routine cervical and breast screening should be continued following NHS Screening Programme guidelines. • Women on HRT should undergo regular basic health checks, including annual measurements of weight and blood pressure. • In menopausal women with low sexual desire for whom HRT with sufficient estrogen intake has not been effective, the consideration of

			testosterone supplementation is an option. • Serum androgen level assessment is unlikely to be helpful in diagnosing hormone-dependent low sexual desire due to the poor correlation between circulating androgen levels and clinical symptoms. • Nevertheless, following best practice recommendations from the Global Consensus Position Statement on the Use of Testosterone Therapy for Women, checking testosterone levels is advised to rule out high baseline levels and prevent excessive replacement. • When assessing total testosterone levels, it's important to maintain them within the physiological threshold for females. • Women under the age of 40 who exhibit symptoms indicative of premature ovarian insufficiency (POI) should undergo follicle-stimulating

			hormone (FSH) level measurement as part of their evaluation. • Women diagnosed with premature ovarian insufficiency (POI) should be counseled to undergo hormone replacement therapy, and this treatment should be continued until at least the natural age of menopause, unless contraindicated. • Hormone replacement therapy (HRT) and combined contraceptive pills containing ethinyl estradiol are both viable options for hormone replacement. However, HRT may offer greater benefits for bone health and blood pressure, and it may be associated with lower cardiovascular risk compared to the combined oral contraceptive pill. • Women experiencing early menopause (aged 40-45 years) should receive information and support similar to women with premature ovarian insufficiency (POI).

			They should be advised to consider hormone replacement therapy, which should be continued until at least the natural age of menopause. • Referring to or seeking advice from a specialist menopause service should be considered when specialized input related to menopause is needed.

Appendix C. MeSH Terms PubMed

C.1 PubMed Search for Menopause:

Query	Search Details	Filters	Results
(Menopause[MeSH Terms]) OR (Change of Life, Female[Title/Abstract])	("menopause"[MeSH Terms] OR (("change"[All Fields] OR "changed"[All Fields] OR "changes"[All Fields] OR "changing"[All Fields] OR "changings"[All Fields]) AND "of life female"[Title/Abstract])) AND ((y_5[Filter]) AND (guideline[Filter]))	Guideline, in the last 5 years	52

Appendix D. Treatment Algorithm

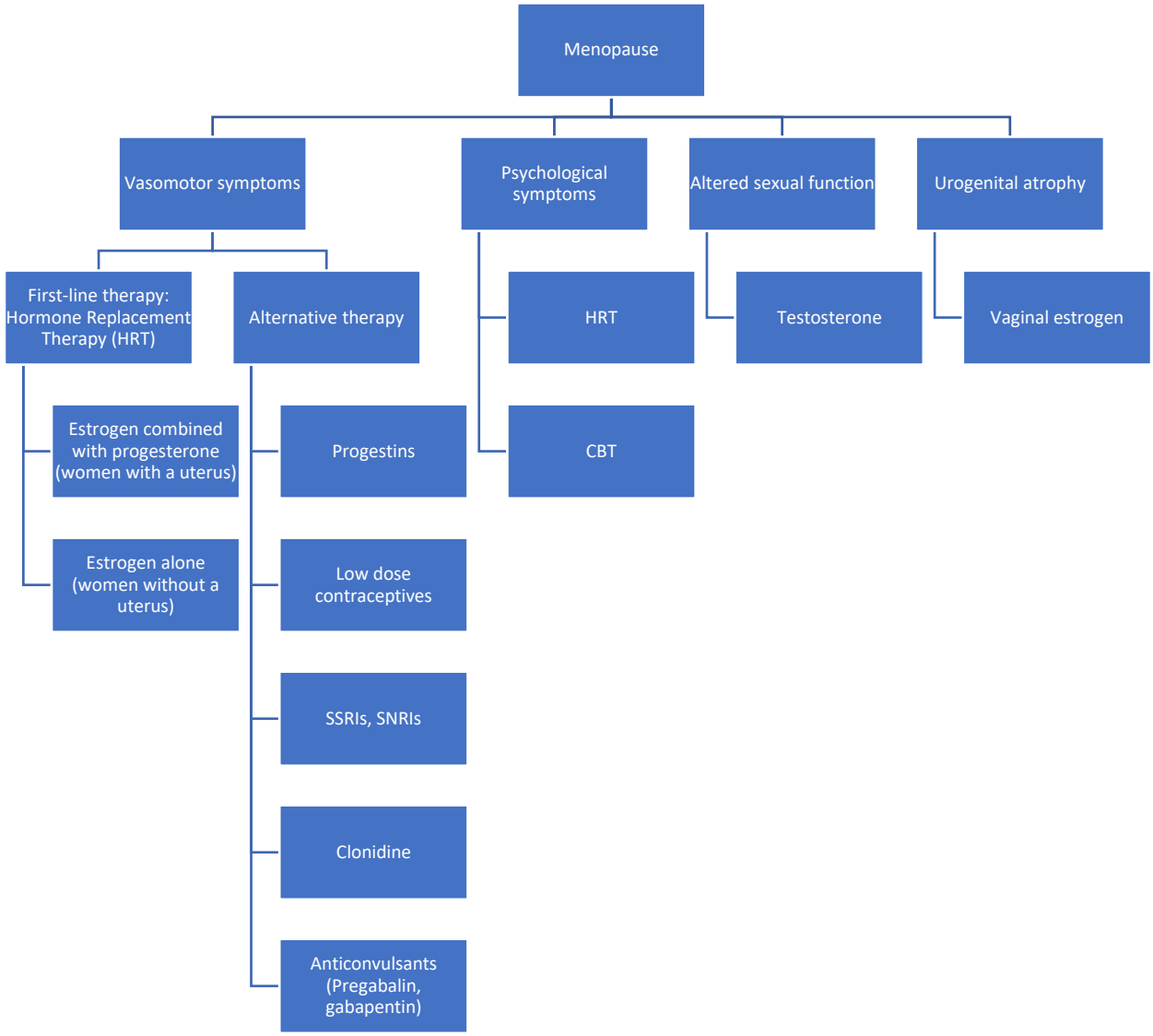

Figure 1. *Treatment Algorithm for the Management of Menopause*