Open Access

OBM Geriatrics

LIDSEN Publishing Inc.

Editorial

Treatments and Management of Menopausal Symptoms: Current Status and Future Challenges

Ciro Comparetto [1, *], Franco Borruto [2]

1. Department of Obstetrics and Gynecology, San Paolo Private Clinic, Pistoia, Italy; E-Mail: cicomp@tin.it
2. Consultant in Health Policy of the Government, Monaco; E-Mail: fborruto@libello.com

* **Correspondence:** Ciro Comparetto; E-Mail: cicomp@tin.it

Special Issue: Treatments and Management of Menopausal Symptoms: Current Status and Future Challenges

OBM Geriatrics
2023, volume 7, issue 3
doi:10.21926/obm.geriatr.2303248

Received: August 31, 2023
Accepted: August 31, 2023
Published: September 13, 2023

Abstract

In the United States (US), menopause occurs at an average age of 52. Menopausal symptoms tend to be maximal during the few years before and the year after menopause (during perimenopause), except for symptomatic vulvovaginal atrophy, which may worsen over time. Up to 20% of bone density loss occurs during the first 5 years after menopause, followed by an age-related bone loss rate similar to that in men. Menopause should be considered confirmed if an age-appropriate woman who is not pregnant has not had a menstrual period for 12 months. Regarding treatment, for vaginal dryness or dyspareunia due to menopause, vaginal stimulation and vaginal lubricants and moisturizers are recommended, and if these are ineffective, low-dose vaginal estrogen, in the form of creams, tablets, suppositories, or rings should be considered; other options include oral ospemifene or intravaginal dehydroepiandrosterone (DEHA) suppositories. Before prescribing hormone replacement therapy (HRT) and periodically while therapy continues, women should be informed of risks (e.g., deep vein thrombosis [DVT], pulmonary embolism [PE], stroke, breast cancer, gallbladder disease, and urinary incontinence); potential harms are greatest for women who start HRT after 60 years of age or who are 10-20 years past menopause onset. If women choose HRT to relieve hot flushes, estrogen plus, a progestin or conjugated

estrogen/bazedoxifene could be prescribed for women who still have the uterus. Treatment with HRT should be tailored to maximize benefits and minimize harms, and periodically benefits and harms should be reassessed; low-dose transdermal HRT may lead to a lower risk of DVT and stroke. Selective serotonin reuptakereuptake inhibitors (SSRIs), selective serotonin-nor-epinephrine reuptake inhibitors (SNRIs), and gabapentin could be considered as less effective alternatives to HRT for relieving hot flushes; paroxetine 7.5 milligrams (mg) is the only non-hormonal drug approved in the US for the relief of hot flushes. Effective non-drug options include cognitive behavioral therapy and hypnosis.

Keywords
Menopause; climacteric; hormone replacement therapy; symptoms; management

1. Introduction

Menopause (from the Greek “μήν” [gen. “μηνός”] month, and “παῦσις”, cessation) is the physiological or iatrogenic interruption of menstruation (amenorrhea), due to reduced ovarian function. Menopause is a natural passage in every woman’s life: the term designates the end of the menstrual cycle and the female reproductive life. Specifically, menopause is defined retrospectively: a woman is considered to be in menopause when 12 months have passed since her last menstrual period [1, 2]. The period in which the woman lives in the state of menopause includes a good part of her overall life:, if on the one hand the average life expectancy is getting higher, on the other hand menopause onset continues to be at the same age. This entails an ever greater expansion, in recent years but also the future, of the time in which the woman lives her life in menopause [3].

Menopause generally occurs between the ages of 45 and 55 years, but it can also occur before the age of 45 (in this case we will speak of early menopause) or after (late menopause), which are not uncommon. Early menopause can also be the result of a hysterectomy with bilateral oophorectomy. In the United States (US), the average age of physiological menopause is 52 years. Smoking, living at high altitudes, and poor nutrition can reduce age [4]. According to what has come down to us, this age period has not undergone significant changes over time: in fact, even at the time of the Greeks and the Roman Empire the age was around 45 years [5]. There are aggravating factors and risk factors that usually interfere by decreasing the chronological age of this event:

- smoking by women, both active and passive, might cause the woman to anticipate the event by 1.5-2 years: the quantity of intake (number of cigarettes) and the duration of intake are closely related to the decrease in age concerning the event; in practice, the more women smoke and the longer they smoke, and the more menopause will occur earlier than expected [6];
- type of diet, which can be considered unsuitable due to the subject’s economic conditions;
- body mass index (BMI), if it is lower than ideal [7];
- alcohol abuse [8]; and
- short stature [9].

By “perimenopause” we mean the years preceding (the duration is widely variable) and the year following the last menstruation. This is typically the most symptomatic stage because hormones

fluctuate. Ovarian activity begins to decrease until the menstrual cycle completely stops. During the first phase of this period, premenopause, the activity of the ovaries begins to wear out: more and more frequently, the menstrual cycles will be anovulatory and both the duration and the extent of the flow will be modified. The observed changes result from the reduction the menstrual cycle, estradiol and progesterone. The cycles become less and less frequent until they are completely absent [10]. Variations in the menstrual cycle usually begin during a woman's 40s, with variations in cycle length. "Menopausal transition" refers to the years in perimenopause leading up to the last period; it is characterized by changes in the menstrual cycle and is divided into initial and final phases (Table 1). A persistent difference in consecutive menstrual cycle length of ≥7 days defines "early menopausal transition". Missing ≥2 cycles define "late menopausal transition". Menopausal transition lasts 2-5 years; it lasts longer in women who smoke and in women who are younger at the onset of menopausal transition. "Postmenopause" refers to the time after the last menstrual period, divided into initial and final stages. In this phase all hormones, including androgens, will be very low.

Table 1 Stages of menopause.

Characteristic	Early transition of menopause	Late transition of menopause	Early post-menopause		Late post-menopause
Duration	Variable	1-3 years	2 years	3-6 years	Till death
Period	Variable length (a persistent ≥7 day difference in the length of consecutive cycles)	Interval of amenorrhea lasting ≥60 days	—	—	—
Follicle-stimulating hormone (FSH) level on cycle days 2-5	High but variable	High (>25 IU/l)	High but variable	Stabilizes at high level*	—
Symptoms	—	Vasomotor symptoms that may occur	Vasomotor symptoms most likely occur	—	Symptoms of genitourinary syndrome of menopause

*Levels of FSH increase until about 2 years after the last menstrual period, and then levels off.

In summary, these are the definitions of the various menopausal phases:

- Premenopause: the time before the last period;
- Postmenopause: the time after the last period;
- Perimenopause: a longer period than premenopause, which ends after one year at the time of menopause; some studies partially disagree, stating that the initial date of this period is around the second half of the fourth decade [11, 12];

- Premature menopause: <40 years of age (age range 40-45 years);
- spontaneous menopause (age range 46-55 years);
- late menopause (>56 years of age group); and
- Artificial menopause: It depends on whether the consequence is direct of some intervention or chemotherapy; hysterectomy, especially in young women, does not deplete ovarian function but yet menstrual cycles cease and in any case women will need additional support in old age [13-16].

As mentioned, menopause is not a disease but a physiological moment in a woman's life. Menopause marks the end of a woman's childbearing age: It is a complex period, not always positively accepted, characterized by a series of signs and symptoms of both physical and psychological nature. The period coinciding with menopause and the months preceding is called "climacteric".

2. Pathophysiology

Menopause is the result of the physiological decline in the synthesis of the female sex hormone (estrogen), essentially linked to aging; the drastic decrease in sex hormones is a consequence of the depletion of ovarian follicles. The production of ovarian follicles is destined to run out in every woman because, unlike men, the number of female gametes is well-defined starting from birth (ovarian reserve). This state causes a series of changes in women concerning the trophic, metabolic, sexual, and psychological aspects, with a series of manifestations (symptoms) that vary according to the person and can be more or less marked, but not all of them can be connected to menopause itself, since other factors such as family and social context influence it [17]. Human beings are not the only animal species subject to this event: the same phenomenon has also been observed in other primates and cetaceans [18, 19].

It is assumed that some chemo- and/or radiotherapy can help anticipate the arrival of menopause; moreover, menopause can be an expression of primary ovarian insufficiency (starting from autoimmune pathologies or genetic predisposition). In this period of life, some women suffer from disorders for which there are treatments and remedies that are useful to guarantee them a good quality of life. A few months before the cessation of menstruation, menstrual cycle alterations are observed (close and abundant or more spaced apart menstruations) [20, 21]. As the ovaries age, their response to pituitary gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) decreases, initially causing the following:

- a shorter follicular phase (with shorter and less regular menstrual cycles);
- reduced ovulation; and
- decreased production of progesterone [22].

During the menopausal transition, abnormal double ovulation and luteal phase events (i.e., the early formation of a follicle due to increased FSH peak during the luteal phase) occur and occasionally they cause higher than normal estradiol levels. The number of viable follicles decreases; finally, the few remaining follicles do not respond, and the ovaries produce reduced estradiol levels. Estrogen is also produced by peripheral tissues (e.g., fat and skin) starting from androgens (e.g., androstenedione and testosterone). However, total estrogen level gradually decreases over the 5 years following menopause, and estrone replaces estradiol as the most common estrogen. As menopause approaches, androstenedione levels drop by half. Reduction in testosterone, which

begins gradually during early adulthood, is not increased during menopause since the stroma of the postmenopausal ovary and the adrenal glands continue to secrete much of it. Reduced levels of ovarian inhibin and estrogen, which inhibit the pituitary release of LH and FSH, also cause a substantial increase in LH and circulating FSH levels. Surface cells in the vagina are shed, leading to a more alkaline potential of hydrogen (pH). As a result, the number of lactobacilli decreases and pathogenic bacteria increase, raising the risk of infection. Premenopause is characterized by the first hormonal imbalances: the plasma levels of inhibin decrease while FSH is found to be more than normal. Other imbalances do not appear: the cycle and the amount of estrogen remain regular up to an age of less than 40 years. Over time, an increase in FSH is observed more and more while the cycles become more and more anovulatory, in the last 30 months before menopause [23].

There are numerous hypotheses as regards the cause of menopause. Some studies have focused on the evolution of FSH and gonadotropins looking for an involvement of the hypothalamic-pituitary axis. However, the most accredited hypothesis is that the cause lies in the ovary itself [24, 25]. In fact, according to this theory, the follicles, subject to deterioration, are chosen by the body itself: the first to be used are the most resistant ones, which must be replaced over the years because they are worn out, but when they are replaced, the new follicles are already damaged: this would lead to follicular depletion-atresia [5].

If it is true that menopause that occurs at the age of 50-51 years can be considered a natural event, albeit with its burden of possible signs, symptoms, and risk factors, premature menopause represents a real hormonal deficiency (premature ovarian insufficiency [POI]) that must be tackled in the same spirit as an endocrine pathology characterized by the lack of hormone production, such as a deficiency of the thyroid gland. The early deficiency of the female hormone estrogen, but also the androgenic deficiency resulting from ovarian failure, are implicated in the onset of more severe symptoms on the vasomotor side (hot flushes), mood, sleep and memory, anxiety-depressive disorders, osteoarticular pain, weight control, and, last but not least, sexuality with decreased sexual desire, poor arousal, and lubrication and orgasm deficiency. But that's not all: numerous studies have shown that POI is associated with a higher mortality rate for all causes, with a greater risk of cardiovascular events (heart attack and stroke) and neurodegenerative diseases (senile dementia and Parkinson's disease), as well as an increased risk of fractures resulting from osteoporosis [26]. In 50% of cases, POI occurs for unknown causes, while it can occur more frequently in patients with autoimmune diseases or who show familiarity (mother and/or grandmother with POI). Not much can be done to prevent it, other than trying to predict it by measuring FSH levels on the third day of the menstrual cycle by combining the follicular count which measures the small follicles, i.e., the so-called "ovarian reserve", a figure which, if measured over time together with another substance produced by the ovary, the anti-Müllerian hormone (AMH), can help to understand if the young woman is losing fertility ahead of normal schedule. This already happens 5-7 years before the last menstrual period, when menopausal symptoms appear, announcing that the time for reproduction has expired. If FSH levels are higher than 30 international units/liter (IU/l) and the cycle has been absent for at least 3 months, one can reasonably think that menopause has arrived and, if hot flushes, insomnia, vaginal dryness, and so on are also associated, it is already advisable to intervene with therapy without waiting for the canonical 12 months that put the definitive menopause passport in the woman's pocket [27, 28].

The most important consequences of the drop in estrogen are: the increase in cardiovascular risk (heart attack, cerebral stroke, and hypertension) and bone and joint diseases, in particular the

increase in the incidence of osteoporosis. Until menopause, women have a lower cardiovascular risk than men because estrogen produced by the ovaries guarantees a lower amount of cholesterol in the blood. Cardiovascular diseases (CVD) are also the main cause of death for menopausal women, far exceeding all neoplasms, including breast cancer. Furthermore, we must not underestimate the increase in body weight, which occurs to a variable extent in all menopausal women and represents a problem in more than 50% of women over 50. Estrogen deficiency conditions, together with age, cause a slowdown of metabolism in general, and increase appetite with an "apple" distribution of body fat, i.e., at the waist level, a typical site of the male sex, which involves greater cardiovascular risk [29]. After menopause, low-density lipoprotein (LDL) cholesterol levels rise in women. High-density lipoprotein (HDL) levels remain about the same as before menopause. The change in LDL levels may partly explain why atherosclerosis and thus coronary artery disease (CAD) becomes more common among women after menopause. However, whether these changes result from aging or declining estrogen levels after menopause is unclear. Until menopause, high estrogen levels can protect against CAD [30]. At the bone level, the absence of estrogen causes a reduction of bone mass and the appearance of osteoporosis is very frequent. Up to 20% of bone density loss occurs during the first 5 years after menopause. After this period of rapid bone loss, the rate of age-related bone loss in women is similar to that in men [31].

Much has been said and written about hormone replacement therapy (HRT) based on estrogen and progestins, sometimes creating unjustified fears about thrombotic and cancer risks. In truth, HRT is the most effective therapeutic tool which, if used at the right time, i.e., when the woman is in the first phase of menopause, can prevent not only the symptoms, but all the most important pathologies that can interfere with healthy longevity. Low doses, natural hormones identical to those produced by the ovary, and personalized therapy schemes based on the characteristics of each woman can help overcome the hormonal change almost without realizing it, preventing the appearance of many risk factors, first of all the increase in cholesterol, blood sugar, insulin resistance, and blood pressure [32]. What is certain, and is defined by important guidelines and scientific consensus documents, is that POI must be treated with HRT up to 50-52 years old to limit the damage of premature hormone deficiency. Over time, it is possible to continue evaluating the risk-benefit ratio annually with a few blood tests and preventive investigations, such as mammography, transvaginal pelvic ultrasound, and computerized bone mineralometry (CBM). Therefore, women must entrust themselves with confidence to an experienced menopause specialist to deal with it in the best possible way, even with a healthy lifestyle and a positive spirit [33-36].

3. Menopause-Associated Symptoms and Diseases

Symptoms that accompany menopause, just like those of premenstrual syndrome, cannot be defined with certainty, since every woman reacts subjectively to this delicate period of life. A decrease in estrogen can cause disturbances and symptoms both of a neuro-vegetative nature (hot flushes, profuse sweating, palpitations and tachycardia, changes in blood pressure, and dizziness) and of a psycho-affective nature (irritability, unstable mood, fatigue, anxiety, depression, difficulty in concentrating and falling asleep, memory disturbances, and decreased sexual desire), together with joint pain, dry skin, vaginal dryness, genital itching, and the so-called "menopausal genitourinary syndrome" [37, 38]. Given that the characteristic symptoms of this period tend to

begin progressively, as already mentioned, the symptoms of menopause can vary from woman to woman in type and intensity. Marked fluctuations in estrogen levels can contribute to other perimenopausal symptoms and signs such as:

- soreness of the breasts;
- changes in menstrual flow; and
- exacerbation of menstrual migraine.

The breasts and skin will also tend to lose elasticity. The symptoms most classically associated with menopause are hot flashes and profuse sweating. Hot flushes, especially if very frequent, are associated with irritability, difficulty concentrating, and frequent nocturnal awakenings, conditions that cause a reduction in quality of life [39]. These symptoms can last from 6 months to >10 years and range from nonexistent to severe. Hot flushes and/or night sweats due to vasomotor instability affect 75-85% of women and usually begin before the end of menstruation. Vasomotor symptoms last an average of 7.4 years and may persist for >10 years in some groups of women [40]. Women feel warm or hot and may sweat, sometimes profusely; basal temperature increases. The skin, especially the face, head, and neck, may become red and warm. The flush, lasting from 30 seconds to 5 minutes, may be followed by chills. Hot flushes can manifest during the night as night sweats. The mechanism of hot flushes is unknown, but it is believed that they result from changes in the thermoregulatory center located in the hypothalamus. Baseline body temperature variation that is comfortable for women decreases; as a result, a small increase in body temperature can trigger heat release as a hot flush.

Female genital organs are greatly affected by the drop in estrogen, and this causes hypotrophy of the labia minora and labia majora. Vaginal mucosa thins and will be characterized by dryness and discomfort during the sexual act. Vaginal symptoms include dryness, dyspareunia, and occasionally irritation and pruritus. As estrogen production decreases, the vulvar and vaginal mucosa become thinner, drier, more flaky, and less elastic, and vaginal wrinkles are lost. Genitourinary syndrome of menopause includes symptoms and signs due to estrogen and androgen deficiency such as:

- vulvovaginal atrophy;
- urinary urgency;
- dysuria; and
- frequent urinary tract infections (UTI) and/or vaginitis [41].

In some cases, the muscles and structures that support the bladder also lose their function, facilitating the onset of urinary incontinence [42].

Finally, psychological alterations are not infrequent: poor concentration, anxiety, depression, irritability, asthenia, low libido, and memory loss are often associated with menopause onset. Many women experience these symptoms during perimenopause and assume menopause is to blame. However, the evidence to support a connection between menopause and these symptoms is mixed. Furthermore, these symptoms are not directly related to decreased estrogen levels with menopause. Recurring night sweats can contribute to insomnia, fatigue, irritability, and poor concentration due to disrupted sleep. However, during menopause, sleep disturbances are common even among women who do not have hot flashes.

Symptoms and clinical signs can also be divided according to the time , thus having immediate, deferred, and late manifestations [11]. As regards immediate manifestations, in addition to the obvious alteration of the menstrual picture (polymenorrhea, oligomenorrhea, hypomenorrhea, and hypermenorrhea), psychological disorders such as anxiety, irritability, nervousness, and dysphoria

are expressed in the immediate phase [43]. Neurologically, we are witnessing an aging of the person, with a consequent decrease in the ability to concentrate and remember. In addition, there is an increase in the weight of the person. Among the minor manifestations, urticaria can also be shown [44].

Among manifestations at the vasomotor level, hot flushes are the most frequent [45]. These are episodes of sudden temperature changes, the woman suddenly begins to sweat and feels hot flushes. These episodes are found in 65-75% of cases and it is no coincidence that it is one of the main symptoms. The percentage changes depending on the area, also due to local eating habits: for example, in Indonesia women who have this disorder are reduced by 20% to 10%, whereas in China the percentage stops at 25% [46, 47]. Clinical studies have also calculated the duration of the phenomenon which rarely exceeds 6 minutes [48]. Generally, it occurs in 20% of premenopausal women even in normal hormonal conditions. The redness involves the head and surrounding parts (face, neck, and nape), while subsequently there is a drop in temperature up to a feeling of cold. As regards duration, both the single manifestation and the frequency with which it appears are considered very variable. Some studies have found a correlation of the frequency with the external temperature: at low temperatures they are less frequent, while at high temperatures the episodes increase [49]. Another correlation has been found during the night, where they contribute to disturbed sleep [50]. Finally, the symptom's duration often persists even for 5 years after menopause (although it generally lasts 1-2 years) [51].

Among psychological factors, the most important remains depression (the calculated average is 50% of women), but the expression of this disorder varies according to ethnicity; for example, it has been shown that, compared to white women, African Americans are more affected by this psychological condition [52, 53]. Among other things, it has been noted how it persists above all at the beginning, when a woman enters the state of menopause, but often there are also relapses of this event [54]. This correlation is also discussed in the case of women who have undergone hysterectomy; some US studies show no association, while other Canadian studies show a worsening of women's depressive state [55, 56]. Among the disturbances related to nocturnal rest, the most frequent is difficulty in falling asleep: in women more frequently we witness restless sleep. It often happens that they wake up during the night, and this state initially worsens, while the most serious sleep disorder is sleep deprivation, insomnia, an anomaly that can be a complication of perimenopause, especially common in Hispanic women [57-60].

Subsequently, changes at the cutaneous level begin, and the epidermis and the dermis become thinner, in the latter case a decrease in collagen is noted. The decrease in collagen in women is calculated at 2.1% per year [5, 61]. These variations cause various atrophies, which not only concern the genitourinary system but also the skin in general, becoming less elastic and dehydrated; this causes an increase in wrinkles and itchy sensations, and arthralgia also occurs at the distal joints (knees, hip, and spine); the incidence is 50% [11, 62]. Many studies have shown that with the hormonal changes of menopause, sexual desire in women decreases. However, studies and interviews confirmed that women are still satisfied with their relationship with their partner even after the menopausal state [63, 64]. Furthermore, there is also an increase in the difficulty in practicing sexual activity (dyspareunia and vaginal pain when attempting penetration is shown), anorgasmia, and burning after intercourse [65-67]. As far as vaginal atrophy is concerned, this event is often accompanied by cystitis and urethritis, it often leads to what is defined as the "urological syndrome of menopause". The following elements characterize this syndrome:

- tenesmus;
- dysuria;
- pollakiuria;
- nocturia (less frequently); and
- negative uroculture.

Given the high sensitivity of the various nerve endings of the apparatus, the passage of urine alone is sometimes sufficient to trigger the syndrome; these disorders are found in 50% of women upon reaching menopause [68].

In the final phase, there are characteristic physical symptoms, among which are muscle pains, a decrease in bone mass at the origin of osteoporosis, and a decrease in physical energy. Recent studies have also found an increase in blood pressure compared to fertile women [69]. When a woman is in the perimenopause period, increased bone resorption is also related to the lack of estrogen [70-72]. Osteoporosis is a reduction in bone density that can easily lead to fractures if subjected to minor traumas. There are two types:

- Type I osteoporosis (also defined as primary), which concerns postmenopause (from the fifth to the seventh decade of age); and
- Type II osteoporosis (secondary), is caused by another pathological state and occurs in youth [73].

Once menopause has been reached, there is an increase in heart disease but the mortality due to this complication is not higher than that of breast cancer [11]. The woman/man ratio changes after the event. First a ratio of 1:5 is shown, then the difference decreases considerably and after 70 years the incidence is identical in both sexes. Leaving aside the consequences of the age factor alone, the decrease in estrogen leads to hyperglycemia, diabetes, hypertension, dyslipidemia, and obesity; they are all dangerous factors for heart work and their cumulative manifestation leads to high cardiological risks. Recent studies have shown that HDL levels decrease and apolipoprotein B values increase during menopause [74].

During the menopausal state, a greater danger has been found with regard to cardiac surgery in general, particularly the one involving the mitral valve: this is always due to the sudden change in hormones in the individual. It has been calculated that women of an age included in the period 40-59 years demonstrate a more than double mortality rate compared to men of the same age; this ratio considerably decreases both before and after this period [75, 76].

For several years, a questionnaire based on a scale of values, called the “menopause rating scale” (MRS), consisting of 10 questions directed to postmenopausal women, was tested in Germany. The subjects had to express, through a graded score from 0 to 4, the intensity of symptoms, complications, and assessments of their state of health, before and after the treatment they received [77]. However, the validity of the questionnaire has been questioned for several years and these concerns have been translated into various languages, from Spanish to English [78, 79].

4. Diagnosis

Diagnosis of menopause is clinical. Perimenopause is likely if the woman is in the appropriate age range and has some symptoms and signs of perimenopause. However, pregnancy should always be considered. Menopause is confirmed when a woman has not had a period for 12 months and there is no other obvious cause. A pelvic examination must be done; the presence of vulvovaginal

atrophy supports the diagnosis. Any abnormal findings (e.g., pelvic masses) should be noticed. FSH levels can be tested, but this testing is rarely needed except perhaps in women who have had a hysterectomy and younger women than the typical menopausal age. Consistently elevated levels confirm menopause. The following postmenopausal women should be screened for osteoporosis:

- women who are at high risk of fracture (e.g., patients with a family history of osteoporosis);
- those who have a history of eating problems, low BMI, chronic use of corticosteroids, gastric bypass surgery, Crohn's disease, malabsorption syndrome, or a previous fragility fracture; and
- all women ≥65 years [80].

For a correct diagnosis, it is necessary to wait 12 months from the last period, but from 6 months onwards the probability is very high [65]. For differential diagnosis, there are several pathological conditions that can lead to menopause-like manifestations [81]:

- thyroid dysfunction (hypothyroidism and hyperthyroidism);
- polycystic ovary syndrome (PCOS);
- carcinoma of the uterus; and
- disorders related to the pituitary gland (hypopituitarism and hyperpituitarism).

In the years following menopause, some clinical tests must be performed on the woman, some annually, others only if certain situations occur. A list of tests to be carried out for control is the following:

- mammography;
- breast ultrasound;
- abdominopelvic ultrasound;
- transvaginal ultrasound;
- glycemia; and
- magnetic resonance imaging (MRI), if the woman experiences certain symptoms (such as abnormal hardening of the breasts).

5. Management

As we have said before, menopause is a normal stage in a woman's life, but every woman has a unique experience. Quality of life may decrease if symptoms are severe or less common symptoms of menopause, such as joint aches and pains, develop. For some women (e.g., those with a history of endometriosis, dysmenorrhea, menorrhagia, premenstrual syndrome [PMS], or menstrual migraine), quality of life may improve after menopause [82]. When symptoms become particularly intense, medical advice becomes essential to affect a woman's quality of life. If he deems it appropriate, this healthcare figure can prescribe drug therapy to the patient whose purpose is to reduce menopausal symptoms. At the same time, pharmacological therapy can be used to prevent the onset of certain pathologies that may be favored by the menopausal state [83]. Discussing the physiological causes of menopause and possible signs and symptoms with women helps them manage the changes that occur. Women who, living in this state, seek relief or a possible cure, are only a very small part, estimated by studies at around 10% [84].

Symptoms can be treated with lifestyle changes, complementary and alternative medicine, and/or HRT. Non-pharmacological options effective in randomized controlled trials (RCT) for treating vasomotor symptoms include cognitive behavioral therapy and hypnosis. These treatments can also improve sleep and sexual function [85]. For hot flushes, it can help:

- avoiding triggers (e.g., spicy foods, lights, comforters, and predictable emotional reactions);
- cool down the environment (e.g., by turning down the thermostat, using fans, and cooling gel pads [gel-filled sheets that are placed on a mattress and dissipate body heat]);
- Wearing layered clothing, which can be removed when needed can help; and
- exercise and weight loss [86-91].

Devices that cool skin receptors may help some women; they can be worn as cuffs or necklaces or placed on the neck's back. Over-the-counter vaginal lubricants and humidifiers help relieve vaginal dryness. Normal intercourse or other vaginal stimulation helps preserve vaginal function. Regular exercise, rhythmic breathing (a slow, deep type of breathing), mindfulness, or relaxation techniques to reduce hot flashes have had mixed results. However, exercise, yoga, and relaxation can improve sleep and reduce stress. Acupuncture causes a notable placebo effect and produces variable results [65, 92-94].

Prevention of cardiovascular and osteoarticular complications can be implemented immediately. The first step is to follow a controlled diet. It is good to favor wholemeal when choosing food, as they are richer in dietary fiber, vitamins, and mineral salts. The guiding principle must be variety in moderation, cutting out excess fat and too salty foods, drinking at least 25 milliliters (ml) of water per kilogram (kg) of body, and giving preference to spices. Obese or over-weighted women need to change their lifestyle and follow a more moderate diet, while the literature discuss the usefulness of some drugs such as orlistat [95-98].

Arthralgia requires a treatment that involves the person in physical activity (such as stretching or a stationary bike). For insomnia, exercise, massage, and avoidance of all forms of stress are recommended, as pharmacological therapy of 300 milligrams (mg) of micronized progesterone is useful for combating sleep-related disorders, as discussed below [99]. Regarding osteoporosis, the literature has always emphasized the importance of preventing this harmful state, therefore it requires cessation of negative vices such as alcohol or cigarettes, physical exercise. However, above all a diet based on a richness of calcium 1000 mg per day (but doses of up to 1500 mg per day can be reached if deemed necessary), at the same time it must be low in caffeine and sodium chloride [100]. As pharmacological treatment as an alternative to estrogen, or if contraindicated, there is calcitonin 10-25 IU per day, a bone resorption inhibitor, studied and tested in the literature for decades [5, 101]. Various types of animal and human calcitonin, but studies assume that non-human ones may induce minor benefits [102]. Other possible drugs are bisphosphonates, such as alendronate and etidronate [103].

To control postmenopausal symptoms, a wide variety of complementary and alternative therapies/non-hormonal drugs or preparations, which have an action similar to that of estrogen, are often used. These are compounds extracted from plants, with a structure similar to estradiol. Their action in the body resembles that of ovarian estrogen given their affinity for estrogen receptors (ER)-beta and ER-alpha. For this reason, they are called "phytoestrogens" or "natural estrogens" (isoflavones, genistein, and daidzein). The best-known and most used is soy. Soy protein, which has weak estrogenic activity, has been studied with variable results; however, a soy product, S-equol, has been reported to relieve hot flushes. The favorable action of isoflavones and soy derivatives on hot flushes is well documented. Studies carried out with these compounds would indicate a positive effect on circulation, a cardioprotective effect, a protective effect against obesity, a protection against the development of metabolic syndromes (such as, for example, diabetes mellitus), a protective effect against the development of breast, and, finally, an anxiolytic and

antidepressant effect [104]. The extracts come from soy and Trifolium pratense plants [105-107]. The use of this substance for the treatment of menopausal disorders arises from the consideration that oriental women (notoriously large consumers of soy) have lower rates of osteoporosis. Yet, soy has proved ineffective in controlling the most frequent symptoms (hot flashes and night sweats), especially over the long term. Furthermore, efficacy on bone has not been demonstrated. The fact that Eastern women consume soy throughout their lives while in the West it is only administered after menopause could be one of the reasons for the lack of action. Other natural remedies that have been proposed are red clover or preparations based on Cimicifuga rubifolia (racemose), a plant native to North America that can especially counteract hot flushes. However, herbal preparations and over-the-counter products appear not to be helpful. Also, some herbal preparations interact with other medications. Because not all complementary and alternative medicine therapies are effective and safe, clinicians need to discuss the risks and benefits of these therapies to ensure women are well-informed [108]. Moreover, there are no studies that certify the results of these long-term treatments. It is still recommended to use only products tested and approved by regulatory agencies. Phytoestrogens, like other substances of natural origin, can often be linked to risks due to lack of control of production processes. This means some products could be over or underdosed, or have poor effectiveness and safety [109-112]. The relief it brings about the administration of vitamin E has been shown to be minimal [113, 114].

In well-designed studies and RCT, selective serotonin reuptake inhibitors (SSRIs), selective serotonin-nor-epinephrine reuptake inhibitors (SNRIs), and gabapentin be moderately effective in reducing hot flashes. A low dose (7.5 mg once daily) of paroxetine (an SSRI) is the only approved non-hormonal therapy used specifically for hot flushes. However, these drugs are less effective than HRT [115]. Other therapies that may be helpful include the anticholinergic drug oxybutynin, stellate ganglion blockade, and neurokinin B antagonists. Kisspeptin and neurokinin B antagonists are non-hormonal treatments that appear to reduce vasomotor symptoms and thus the need for estrogen therapies [116-118].

Regarding treatment of symptoms, it is essential to identify an appropriate and personalized therapy based on the woman's needs. Among the various therapies useful for resolving menopause-associated symptoms, HRT can help and, at the same time, protect against osteoporosis and CVD, if administered correctly, after a thorough clinical examination of the patient. Physicians should always weigh the risk/benefit ratio when prescribing therapy to women with menopausal complaints to help the woman make an informed choice. For many women, appropriate HRT, carefully planned and monitored, can increase life expectancy and significantly improve quality of life in the postmenopausal years. It is possible to make chronic-degenerative diseases, their complications, and cancer preventable [119]. Depending on symptoms and their severity, the physician may decide to prescribe the administration of additional drugs for the treatment of symptoms and disorders that may be associated with the menopausal condition [120].

The ideal therapy can supply estrogen no longer produced by the ovaries, hence the name "HRT". The estrogen used in HRT can be naturally origin, i.e., purified from horse urine, or produced in the laboratory with biotechnological techniques. However, administration of estrogen alone is not safe. From a physiological point of view, estrogen is responsible for the growth of uterine mucosa cells. Normally, this activity is counteracted by the presence of progesterone. If only estrogen is administered, uncontrolled growth of the uterine lining could be observed, increasing the risk of developing cancer. To avoid this eventuality, estrogen administration is also associated with that of

progesterone or progestins. On the other hand, when the woman is hysterectomized, estrogen can be administered alone. There are also formulations containing a molecule, bazedoxifene, a selective ER modulator (SERM) which can replace progestins, limiting the characteristic adverse effects of progesterone (water retention, breast tenderness, and headache) [121]. Low-dose hormonal contraceptives (the "pill") may be helpful in the last few years before menopause. They can effectively eliminate or reduce symptoms such as:

- hot flushes;
- vaginal dryness; and
- mood swings [122].

They can also help manage heavy or irregular periods. However, hormonal contraceptives are contraindicated in smokers, where thromboembolic risk often does not justify the benefit; these drugs, generally to be taken by mouth (but also available in the form of skin patches or vaginal rings), can increase the risk of thrombosis and arterial hypertension, risks that are already higher in smokers. This approach can also be useful in cases of vaginal dryness [123]. To limit the risk of side effects, therapy should begin with low doses of drugs. If, 2 months after the start of HRT, symptoms have not changed satisfactorily, doses should be increased. In general, using low doses of hormones is sufficient to limit hot flashes and genitourinary symptoms. Two different therapeutic schemes may also be indicated: sequential and continuous HRT. In sequential therapy, the physiological release of the two hormones is simulated. Estrogen can be administered continuously for 28 days or from day 1 to day 21. Progestins are instead taken for 12-14 days. A week after discontinuing progestins, bleeding that simulates the menstrual cycle will appear. In continuous HRT, on the other hand, both estrogen and progestins are administered daily. In this case, amenorrhea will be established: this is the therapeutic form indicated in women who no longer want to have a menstrual flow [124].

HRT involves the administration of hormonal drugs in targeted formulations and dosages. HRT can be prescribed in various ways (oral pills, gel, creams, spray, vaginal ring, and transdermal patches). The woman and the physician will evaluate which modality is more accepted and preferred. Classically, both estrogen and progestins are taken orally. In the case of continuous HRT, some formulations contain both hormones in the same tablet. In some cases, the transdermal route, in which patches slowly release the drug, is used instead. This route of administration has proven to be effective in reducing the onset of hot flushes; the risk of adverse events is also reduced. Transdermal therapy is recommended for women with risk factors such as hypertriglyceridemia, hyperglycemia (diabetes), or for smokers [125]. If, on the other hand, the disturbances refer only to the genital area, with vulvovaginal atrophy and consequent dyspareunia, preparations based on hyaluronic acid, estrogen, or androgens can be prescribed by the vaginal route, in the form of gels, creams, or ovules for topical application at the vaginal level. These are useful solutions for solving genitourinary problems [126, 127]. Topical (topically applied) HRT does not resolve hot flushes, but it can act on vaginal dryness; these therapies usually consist of creams with estrogen in small quantities to be applied directly into the vagina [128, 129].

From a general point of view, HRT is considered reasonably safe for some women, but is still associated with possible risks. It is recommended to take the minimum effective dose for the shortest possible time. In particular, research shows that:

- menopausal HRT may be an option for women up to age 59 years, but only up to 10 years after menopause; younger women and those closest to their last period are less likely to have dangerous side effects;
- menopausal HRT reduces symptoms, for example hot flushes, sleep and mood disturbances, and vaginal dryness;
- Hot flushes typically require higher doses of estrogen, such that they affect the entire body;
- for vaginal dryness or discomfort during sexual intercourse, low-dose estrogen administered with topical therapies may be sufficient; and
- estrogen, alone or in combination with progestins, increases the risk of stroke and thrombosis in the blood vessels of the legs and lungs; these are sporadic risks in women between 50 and 59 years of age [130].

The introduction of these hormones makes it possible to counteract many of the symptoms and/or problems deriving from the menopausal state (hot flashes, depression, irritability, insomnia, tachycardia, vaginal dryness, and decrease in bone mass). In terms of benefits, which are defined as systemic, the therapy has an effect on the central nervous system (CNS) which helps the woman sleep better, have a stable mood, improves skin trophism while maintaining collagen density, in addition to genital and bladder trophism, and the maintenance of BMD. However, HRT use is sometimes avoided because it is not without side effects. The most frequently reported adverse effects in HRT are mostly related to progestins, which frequently cause water retention, breast tenderness, headaches, nausea and discharge, and minor vaginal bleeding. However, other risks may be associated with HRT. Hormonal stimulation with estrogen can provoke the uncontrolled growth of uterine mucosa cells and facilitate the onset of endometrial cancer. The risk of developing breast cancer also appears to be increased, but this occurs above all when HRT is continued beyond 5 years. Finally, thromboembolic phenomena and CVD risks increase [131-135].

In summary, among the various harms are:

- increased incidence of stroke (21-29 cases out of 10,000);
- increased incidence of PE (16-34 cases per 10,000);
- increased incidence of dementia (22-45 cases out of 10,000); and
- increased incidence of breast cancer (30-38 cases out of 10,000).

Other increases contrast with:

- decreased incidence of osteoporosis (from 15 to 10 cases per 10,000);
- decreased incidence of colorectal cancer (from 16 to 10 cases per 10,000); and
- reduction of various symptoms [136].

Studies have shown that about heart disease, the benefits of this therapy are 50%, on the other hand, important studies, published in the same year, found that the intervention could instead increase the risk of heart disease [137, 138].

Given the risks described above, HRT is not a possible therapy for all women. Certain requirements must be met. It can be administered to women who have gone through early menopause (before the age of 45 years), even following a hysterectomy. These women will benefit from HRT both in terms of reduction of vasomotor effects and in delaying the occurrence of osteoporosis. In general, for women who enter menopause early, treatment is provided until they reach the average age of onset of menopause (around 48-52 years). Women under the age of 60 who have been menopausal for less than 10 years and who have significant vasomotor disorders are possible candidates for HRT. Also for them, treatment should not be extended beyond 5 years

[139]. The risk and unwanted effects depend on the amount administered and the time of administration: studies have shown that if they are high and are administered for a short time they can cause serious effects [140]. In recent years, the administration methods have changed and new molecules have been discovered that involve a lower risk (reduced by 75%) regarding coagulation and metabolic alterations [5, 141].

Before starting HRT, the physician must carry out in-depth medical history and diagnostic investigations. Some women have relative or absolute contraindications to HRT. Therefore, HRT must be prescribed and taken under a specialist's supervision and after evaluating its use's pros and cons. Patients with premature menopause and/or who report a reduced quality of life due to one or more symptoms of menopause can benefit from HRT. It is also indicated if there is a clinical picture of decreased bone mass (osteoporosis). Of course, women who do not benefit from the so-called "natural therapies" are also candidates for actual HRT [142]. Absolute contraindications to HRT use are a history of a previous thrombotic disease. Therefore it will be necessary to evaluate age, possible obesity, immobilization, or recent surgery (all factors that can favor the onset of venous thrombi), and evaluate the coagulation structure. On the other hand, absolute contraindications occur when the woman has had abnormal uterine bleeding (AUB) or hormone-dependent ovarian, uterine, or breast cancer. Before starting HRT, the necessary diagnostic tests must be carried out to rule out the presence of small tumor formations that could grow with hormone treatment: pelvic exam, Papanicolaou (Pap) test, transvaginal ultrasound, and mammography are then performed. In these patients, HRT use is precluded and it will be necessary to resort to alternative, non-hormonal therapies [143]. Then, there are relative contraindications, which must be evaluated on a case-by-case basis with the specialist, who will have to balance the advantages and disadvantages of each patient. Women who have suffered from gallstones should start HRT carefully, due to the risk of developing a new biliary colic [144]. In women with previous endometriosis or symptomatic myomas, HRT is not contraindicated but the dosage must be modulated on a case-by-case basis [145]. Before taking HRT, a gynecological evaluation is therefore necessary to evaluate the benefits and risks of therapy itself: during the visit, the specialist notes the woman's clinical history (age, menopause onset, reported complaints, and any side effects for past use of hormonal therapies, such as the contraceptive pill) and her family's history to assess the presence of any cardiovascular, oncological, and osteoporotic risk factors. Once it has been established that HRT can be started, annual gynecological check-ups should be scheduled for the woman on therapy [146]. The assessment of the woman's general state of health is essential for deciding whether or not to prescribe HRT, bearing in mind that this is not the only possible therapy in menopause [147].

HRT improves the quality of life of many women by relieving their symptoms, but it does not improve the quality of life for asymptomatic women. It is therefore not routinely given to postmenopausal women. If HRT is needed to control menopausal symptoms, physicians should determine the most appropriate type, dose, route of administration, and duration, based on treatment goals and individual health risks. Any benefits and harms due to HRT should be periodically reevaluated. For healthy women <60 years or <10 years after menopause onset, the potential benefits of HRT are more likely to outweigh the potential harms. If such women are at risk of bone loss or fracture, HRT reduces bone loss and fracture incidence and can be used in women not candidates for first-line osteoporosis medications. Initial HRT is generally not recommended in women >60 10-20 years after menopause onset. In these women, the potential harms of HRT (e.g.,

CAD, stroke, venous thromboembolism [VTE], and dementia) may outweigh the potential benefits. Unless the clinical recommendation is clear, a consensus decision is advisable for the following reasons:

- The potential benefits and harms of HRT can be complicated;
- The net benefit and harm may be marginal; and
- Health risks can change over time [148, 149].

Estrogen can be administered orally, transvaginally, transdermally, and even intranasally (for estradiol alone):

- Orally:
  - estradiol valerate (2 mg per day); and
  - estriol (1 mg per day); and
- Transvaginally: the same products to which promestriene is added.

Estrogen is used on its own for women who have had a hysterectomy. Oral, transdermal (patches, lotion, spray, or gel) formulations, or vaginal forms may be used. Treatment should start with the lowest dose; the dose is increased every 2-4 weeks as needed. The doses vary about the preparation. Low doses include:

- 0.3 mg orally once a day (conjugated equine or synthetic estrogen);
- 0.5 mg orally once a day (oral estradiol); and
- 0.025-0.375 mg/day delivered from a patch applied to the skin 1 or 2 times/week (estradiol patch).

Women who still have the uterus must be given progestins in addition to estrogen because estrogen alone increases the risk of endometrial cancer. Progestins are often administered in combination with estrogen to provide a more complete treatment, it happens that they are also used alone for endometrial cancer prevention (if they use tamoxifen) or to contrast the symptoms connected to vasomotor disorders. Depending on the administered doses, they produce different effects on estrogen: with low doses they weaken the response of cells to the stimuli imposed by estrogen, at high doses they cause cytotoxicity because they completely block the production of sex steroids in the body:

- Orally:
  - cyproterone acetate, 1 mg per day, also used in the presence of diabetes mellitus [150]; and
  - dydrogesterone, 10-20 mg per day, which in combination with estrogen appears to provide good endometrial protection [151]; and
- transvaginally:
  - Micronized progesterone, 100-200 mg per day, sometimes 300 mg.

Progestins are taken with estrogen continuously (i.e., daily) or sequentially (from 12 to 14 consecutive days every 4 weeks). The dose is:

- Medroxyprogesterone acetate (MPA): 2.5 mg for daily use and 5 mg for sequential use (10-20 mg per day, maximum dose 100 mg per day);
- Nomegestrol acetate: 2.5-5 mg per day; or
- micronized progesterone (natural rather than synthetic progesterone): 100 mg daily and 200 mg for sequential use.

Bleeding due to progestin withdrawal is less likely with continuous therapy, although irregular bleeding may occur during the first 6 months of therapy. Combined products of estrogen and progestins are available as:

- pills (e.g., conjugated equine estrogen [CEE] 0.3 mg plus MPA 1.5 mg once a day; norethisterone acetate [NETA], discovered in 1951, 0.1 mg plus estradiol 0.5 mg or 1 mg once a day; estradiol 1 mg plus progesterone 100 mg once a day; estradiol 1 mg plus drospirenone [DRSP] 0.5 mg once a day; and estradiol 0.5 mg plus DRSP 0.25 mg once a day); and
- patches (e.g., estradiol 0.045 mg plus levonorgestrel [LNG] 0.015 mg/day released from a patch applied to the skin once a week and estradiol 0.05 mg plus NETA 0.14 mg or 0.25 mg per day released from a patch applied 2 times a week) [152].

Combined CEE/bazedoxifene is an alternative. Bazedoxifene protects the uterus; therefore, progestins are not needed. Benefits of CEE/bazedoxifene include a lower incidence of breast tenderness and bleeding compared with other forms of HRT; the incidence is similar to that of placebo. Breast density and breast cancer incidence did not increase in women who were followed up for 2 years [153]. CEE/bazedoxifene may relieve hot flushes, improve sleep, prevent bone loss, and reduce symptoms of vaginal atrophy. The risk of VTE is similar to that with estrogen, but CEE/bazedoxifene appears to protect the endometrium and potentially the breast. Bazedoxifene as a single drug is not available in the US.

When the only symptoms are vaginal, a low dose of vaginal estrogen is preferable. Topical forms (e.g., creams, vaginal tablets, suppositories, or rings) may be more effective for vaginal symptoms than oral forms. Vaginal pessaries, suppositories, or rings that contain low doses of estradiol, e.g., 10 micrograms (mcg) for pessaries, 7.5 mcg for rings, and 4 mcg and 10 mcg for vaginal suppositories, deliver less estrogen to the systemic circulation. Vaginal estrogen at the lowest recommended dose does not require progestins. Higher doses of vaginal estrogen can provide as much estrogen as oral or transdermal therapy and, when given to women who still have the uterus, require the addition of progestins. Any vaginal bleeding in women taking HRT should be evaluated immediately to rule out endometrial cancer. If symptoms are mild, over-the-counter non-hormonal treatments (e.g., vaginal lubricants and moisturizers) may suffice [154]. After consulting their oncologist, small amounts of topical estradiol can be used for women at high risk of breast cancer [155].

For moderate to severe symptoms, treatments include:

- a SERM (e.g., oral ospemifene);
- intravaginal estrogen;
- intravaginal dehydroepiandrosterone (DEHA); and
- Systemic HRT [156].

When using low-dose vaginal estrogen or DEHA or ospemifene, progestins are not needed; however, there are no data on long-term endometrial safety for these drugs. Intravaginal DEHA can relieve vaginal dryness and other symptoms of vaginal atrophy; it is available and effective for relieving dyspareunia due to menopause and is under study as a treatment for sexual dysfunction in women [157].

Progestins (e.g., MPA 10 mg orally once a day or 150 mg depot intramuscular once a month, megestrol acetate [MGA] 10-20 mg orally once a day, and progesterone 300 mg per day evening) are sometimes used only to relieve hot flushes when estrogen is contraindicated. However, they are not as effective as estrogen for hot flushes and do not relieve vaginal dryness. Micronized progesterone can be taken at 100-300 mg at bedtime. Drowsiness may occur. Micronized

progesterone in peanut oil is contraindicated in women allergic to peanuts. The new product combinations do not contain peanut oil.

Estrogen therapy has beneficial effects on bone density and reduces the incidence of fractures in postmenopausal women (not particularly in those with osteoporosis). In one large study, HRT reduced the incidence of fractures by 24% [138]. Nonetheless, estrogen therapy (with or without progestins) is usually not recommended as first-line treatment or as prophylaxis for osteoporosis. When osteoporosis or osteoporosis prevention is the only concern, clinicians should consider initiating HRT if the following conditions apply:

- women are at significant risk of osteoporosis;
- they choose not to take first-line drugs for osteoporosis; and
- they are <60 years old <10 years after menopause onset.

As we have mentioned, the risks of estrogen therapy and combined estrogen/progestins therapy include:

- endometrial cancer, especially if women who have the uterus take estrogen without progestins;
- breast cancer;
- DVT;
- PE;
- stroke;
- CAD;
- dementia;
- gallbladder disease; and
- urinary incontinence.

The risk of endometrial cancer is higher in women with a uterus and are given unopposed estrogen therapy. However, any vaginal bleeding in a woman on HRT should be evaluated immediately to rule out endometrial cancer. Breast cancer risk increases after 3-5 years of combination therapy when the standard dose (e.g., CEE 0.625 mg and MPA 2.5 mg per day) is used.

The most comprehensive data on the benefits and harms of HRT come from two RCTs sponsored in the US by the National Institutes of Health (NIH) as part of the Women's Health Initiative (WHI):

- The WHI Estrogen-plus-Progestin Study, in which women with preserved uterus were randomized into two groups, one treated with a placebo, and the other with a compound containing estrogen and progesterone [158]; and
- In the WHI Estrogen-Alone Study, women without the uterus were randomized into two groups, one treated with a placebo and the other with a compound containing only estrogen [158].

The two studies involved over 27,000 healthy women aged 50 to 79 at treatment initiation. Although both studies were stopped early (in 2002 and 2004, respectively), once it was understood that both therapies were associated with specific health risks, monitoring of participants continued to identify other health effects of HRT.

The WHI Estrogen-plus-Progestin study demonstrated that women taking combination therapy enjoy the following benefits:

- A reduction of one-third of fractures of the hips and vertebrae compared to women treated with placebo: in absolute terms, there were 10 fractures per 10,000 women per year in

women receiving HRT compared with 15 fractures per 10,000 women per year in women receiving placebo; and

- A reduction of one-third of colorectal cancer cases compared to women treated with placebo: in absolute terms, there were 10 cases of colorectal cancer per 10,000 women per year in women receiving HRT compared with 16 cases per 10,000 women per year in women receiving placebo.

However, it should be remembered that monitoring over time has found that neither benefit persists once combined HRT is discontinued.

Women taking only estrogen report the following benefits:

- A one-third reduction in hip and vertebral fractures compared to women treated with placebo: in absolute terms, there were 11 hip and 11 vertebral fractures per 10,000 women per year in women on HRT compared with 17 hip and 17 vertebral fractures per 10,000 women per year in women on placebo; and
- A 23% reduction in breast cancer compared to women treated with placebo: in absolute terms, there were 26 cases of invasive breast cancer per 10,000 women per year on HRT compared with 33 cases per 10,000 women per year in women receiving placebo.

After 10.7 years of monitoring, however, the risks of hip fractures were slightly higher in the group treated with estrogen, while the risk of breast cancer remained lower in treated women than in the placebo group. Even after discontinuing therapy, the increased risk of breast cancer development may persist for a decade, with an entity proportional to the duration of drug intake. However, it should be noted that, to better understand the risk, overweight/obesity and alcohol consumption are factors with a greater impact than taking HRT, which remains a potentially advantageous option after a careful risk assessment. Before initiating the WHI studies, estrogen-only HRT was known to increase endometrial cancer risks in women with preserved uterus. This was why the WHI studies used combination therapy in women with an intact uterus and estrogen-only therapy in women without a uterus.

So, data from the WHI studies have shown that menopausal HRT is associated with the following problems:

- Urinary incontinence: Taking estrogen with progesterone increases the risk of urinary incontinence;
- dementia: Estrogen combined with progesterone doubles the risk of developing dementia starting at age 65 years;
- strokes, thrombosis, and heart attacks: Both combination therapy and estrogen alone are associated with increased risks of strokes, thrombosis, and heart attacks; regardless of therapy, however, the risk normalizes when therapy is stopped;
- breast cancer: women treated with estrogen and progesterone are slightly more likely to be diagnosed with breast cancer; in these women, at the time of diagnosis, cancer was larger and more likely to have infiltrated lymph nodes; the number of breast cancers in women receiving combination treatment increased with the duration of treatment and decreased after discontinuation of therapy; these studies have also shown that both therapies (estrogen-only and estrogen with progesterone) reduce the ability to diagnose early breast cancer through mammography; women on HRT underwent more mammography checkups for abnormalities detected on screening mammography and more biopsies; breast cancer mortality in the group of women treated with estrogen and progesterone was 2.6 per 10,000 women per year

compared with 1.3 per 10,000 in the placebo group; overall mortality in the group of women treated with estrogen and progesterone after a diagnosis of breast cancer was 5.3 per 10,000 women per year compared with 3.4 per 10,000 in the placebo group;

- Lung cancer: The risk of lung cancer was equal in women on HRT and the placebo group; however, women on HRT who were diagnosed with lung cancer were more likely to die from cancer. There was no difference in the number of cases or deaths from lung cancer between the estrogen-only group and the placebo group, and
- colorectal cancer: initial study report data showed a lower risk of colorectal cancer in women treated with combination therapy compared to women receiving placebo. However, colorectal cancers seen in treated women were in more advanced stages at the time of diagnosis; there were no differences in either risk or stage of colorectal cancer at diagnosis between women treated with estrogen alone and placebo; a subsequent analysis of the WHI studies found no data to support that estrogen alone or the combination of estrogen and progesterone have any effect on colorectal cancer risk, tumor stage at diagnosis, or mortality from colorectal cancer.

When estrogens are used alone, the risk of breast cancer was slightly lower at 7 years in the WHI studies, but this benefit seems to disappear after 10-15 years of use [159]. The risk of VTE and stroke may be lower when low-dose transdermal estrogens are used. Older postmenopausal women (>10 years after menopause or >60 years when starting HRT) have a higher risk of CAD and dementia when given combination therapy. The incidence of gallbladder disease and urinary incontinence may be increased by combination therapies or estrogen alone. The risk of these disorders is very low in healthy women who take HRT for a short time after menopause. Progestins may have adverse effects (e.g., abdominal bloating, breast tenderness, increased breast firmness, headache, and increased LDL cholesterol levels); micronized progesterone appears to have fewer adverse effects. Progestins may increase the risk of thrombosis. There are no long-term safety data on progestins. Before prescribing HRT, and periodically as therapy continues, physicians should discuss the risks and benefits with women [160, 161].

SERMs (see below) tamoxifen and raloxifene have been used primarily for their anti-estrogen properties and not for relieving menopausal symptoms. However, ospemifene, another SERM, can be used to treat dyspareunia due to vaginal atrophy if women cannot use estrogen or a vaginal medication (e.g., if they have severe arthritis) or if they prefer to use an oral drug other than estrogen; the dose is 60 mg orally once a day [162]. Hot flushes may temporarily increase in women who have recently taken HRT, but in most women, hot flushes resolve after about 6 weeks. Bazedoxifene is administered with CEE; it can relieve hot flushes, improve sleep, prevent bone loss, and reduce symptoms of vaginal atrophy.

As we have said before, up until menopause, women are generally more protected from CVD, such as heart attack or stroke, as well as neurodegenerative diseases, such as Alzheimer's. Immediately after menopause onset, the increase in cases of these pathologies seems to be associated with the sudden reduction in estrogen levels. HRT had therefore been welcomed with great favor and the hope that it could prevent CVD onset in women who used it. But, after the initial enthusiasm, data were published, obtained from the WHI, which not only denied the protective effect of this therapy, but even showed how cardiovascular risk, in women who used HRT, was increased, as was the risk of developing breast cancer in women who used estrogen combined with progesterone. After an initial surprise, new analyses of the WHI study have brought to light very

interesting data. Cardiovascular risk increased only in women who started therapy after several years, more than 10, from menopause onset; if therapy, on the other hand, began within the first few years of menopause, the possibility of developing heart disease was reduced. Hence, the hypothesis of the "window of opportunity" was born. The earlier the therapy was started, the lower the cardiovascular risk. The risk of developing breast cancer was also not increased when treatment was less than 4 years.

A similar argument can be made on the onset of neurodegenerative diseases. Changes in hormone levels observed in women after menopause would be among the factors favoring the onset of diseases such as Alzheimer's. However, the first studies showed no benefit and even a greater decline in cognitive functions could be observed if HRT was started after the age of 65 years. Recently, new analyses with retrospective studies have instead highlighted the efficacy of HRT in preventing the late onset of various neurodegenerative diseases (Alzheimer's, but also Parkinson's and dementia not associated with Alzheimer's). The authors suggest that the targeted use of HRT in still apparently healthy women (over the age of 45 years) could prevent, but not cure, degenerative diseases. Despite the promising results of this and other studies, we still need to evaluate with caution the possibility of using HRT to prevent neurodegenerative diseases [163].

As a result of these findings, the number of women taking HRT dropped precipitously [164]. Based on all this information, the way HRT is prescribed has changed. Today, HRT is prescribed only for those women who have recently entered menopause, who have not had previous VTE or CVD, and, in any case, never for women over 65. Where possible, topical vaginal therapy is preferred and low-dose drugs are used for the shortest possible time. As with many treatments, the balance between risk and benefit should be duly weighed [138]. The WHI recommends that women with non-surgical menopause take the lowest possible dose of HRT for the shortest possible time, in order to minimize the associated risks. The current indications formulated by the Food and Drug Administration (FDA) include the short-term treatment of menopausal symptoms, such as hot flushes or urogenital atrophy, and the prevention of osteoporosis. In 2012, the US Preventive Services Task Force (USPSTF) concluded that the harmful effects of combining estrogen and progestins will likely outweigh the disease prevention benefits in most women [165-167].

A study published by the Endocrine Society (ES) stated that if taken during perimenopause, or in the early years of menopause, HRT carries significantly fewer risks than previously published and reduces mortality for most patients. The American Association of Clinical Endocrinology (AACE) also released a position statement in 2009 approving HRT in certain clinical scenarios. Not all menopausal women need HRT. This is usually recommended in the following cases [168]:

- early menopause;
- induced or artificial menopause;
- high sexual difficulties due to atrophy and narrowing of the vagina, with burning and pain;
- high bone fragility;
- risk of osteoporosis;
- high risk of heart disease;
- high frequency and intensity of hot flushes, to prevent a woman from a normal life; and
- severe mood swings [169].

There is an alternative to HRT. SERMs – such as raloxifene – are used to prevent treat osteoporosis in postmenopausal women. Indeed, in this category of patients, the risk of developing osteoporosis due to a decrease in bone mineral density (BMD) can be very high. Tibolone limits the

symptoms of menopause and slows down osteoporosis onset, while avoiding the risk of uterine cancer. A particularly useful drug is ospemifene, used to treat genitourinary disorders when estrogen therapy cannot be used. The drug can stimulate the growth of vaginal epithelial cells without stimulating the activity of ER in the breast. To treat hot flashes, some drugs typically used for depression are useful: SSRIs and SNRIs, drugs capable of blocking the uptake of a neurotransmitter, serotonin. Generally, these drugs are used at lower dosages than those normally used for depression and the results are seen after 2-3 weeks [170-172]. SERMs have a particular estrogenic function, in fact they manage to modulate their functions at both the tissue level and the organs involved. The most used are:

- Tibolone (2.5 mg dose per day), which leads to a decrease in cholesterol, used above all in the case of hypertensive women, also combats vaginal atrophy and hot flushes [173, 174]; and
- Others are veralipride, bromocriptine, clonidine, effective against headaches and hot flushes, and methyl-dopa which works on alpha-adrenergic receptors [175].

Among these are phytotherapeutics (phyto-SERMs) which have both agonist and antagonist actions on estrogen; all SERMs tend to decrease cholesterol [176-179]. The most used are:

- Raloxifene (60 mg per day) only exerts protective effects on the breast and endometrium [180]; this active ingredient also fights osteoporosis, but its correlations with PE and increased thrombotic risk are not clear [181]; and
- Tamoxifen has a dual action: on the one hand it prevents osteoporosis, while on the other hand its opposite action manages to partially prevent breast cancer, and it also provides results in some possible complications such as fibromyalgia [182-184]; its main side effects are hot flushes [185].

Other SERMs under study are [186]:

- Dioxide: it has an estrogen-like effect on bones and lipid metabolism and has an anti-estrogenic effect on the breast and uterus [187];
- GW 5638b: it has an estrogen-like effect on bones and lipid metabolism and has an anti-estrogenic effect on the breast and uterus;
- EM 800b: it has an estrogen-like effect on bones and lipid metabolism and has an anti-estrogenic effect on the breast and uterus;
- Resveratrol: it has an estrogen-like effect on bones and lipid metabolism and has an anti-estrogenic effect on the breast and uterus; the literature on resveratrol in menopause suggests a possible cardioprotective role in both pre-and postmenopausal women, due to its action on lipids and oxidative stress; an Australian study demonstrates an improvement in circulatory flow [188, 189]; furthermore, it improves the skin response to menopause due to a collagenase-inhibiting action; it has recently been understood that resveratrol exerts its effects on the skin, in addition to the well-known antioxidant-type mechanism, also through an anti-apoptotic mechanism and inhibiting the action of type 3 caspase through a direct action on specific receptors of the epidermis to polyphenols recently identified on an in vitro experimental model [190]; and
- ICI 182, 780 (fulvestrant): it has an anti-estrogenic effect on the breast and uterus [191].

6. Guidelines

The average age of menopause in the United Kingdom (UK) is 51, although 1% of women experience POI. Eight out of 10 women suffer from perimenopausal symptoms, among which the most common are hot flushes and night sweats that persist for about 4 years, also significantly influencing quality of life [40, 192]. There is great variability in the provision of services and information for postmenopausal women in the UK and the use of HRT has been hotly debated [193, 194].

These are the most recent recommendations from the National Institute for Health and Care Excellence (NICE) on the diagnosis and treatment of menopause [195, 196]. NICE recommendations are based on a systematic review of the best available evidence and explicit consideration of the cost-effectiveness of health interventions. When the evidence is limited, recommendations are based on the experience of the group that produced the guideline – the Guidelines Development Group (GDG) – and on the rules of good clinical practice. Evidence levels of clinical recommendations are indicated in italics in square brackets:

1. Individualized assistance:
   - Take an individualized approach to all levels of menopausal diagnosis, investigation, and treatment;
     [based on the experience and opinion of the GDG]
2. diagnosis:
   - diagnose menopause in healthy women aged >45 years who:
     - have amenorrhea for at least 12 months and are not using hormonal contraceptives; or
     - are hysterectomized and show menopausal symptoms (e.g., vasomotor, musculoskeletal, and urogenital symptoms, mood alterations, and sexual problems); and

     [based on very low to moderate quality evidence from observational studies and the experience and opinion of the GDG]
   - consider FSH dosage to diagnose menopause only in women:
     - aged 40 to 45 years with menopausal symptoms (including menstrual cycle changes) or in women <40 years of age in whom menopause is suspected; and
     - who are not taking estrogen-progestins contraceptives or high doses of progestins;

     [based on very low to moderate quality evidence from observational studies and the experience and opinion of the GDG]
3. information and advice:
   - provide women with information including:
     - an explanation of the stages of menopause: perimenopause and postmenopause;
     - common symptoms and diagnosis;
     - lifestyle changes and interventions that can improve a woman's well-being and general health status: smoking cessation, advice on exercise and diet, and screening for breast and cervical cancer;
     - benefits and harms of hormonal, non-hormonal, and non-pharmacological treatments for menopausal symptoms;
     - contraception; and
     - long-term effects of menopause, such as osteoporosis; and

[based on very low to low-quality evidence from qualitative research studies and the experience and opinion of the GDG]

- offer support and information about menopause and fertility to women who are likely to enter menopause following medical or surgical treatments;
  [based on very low to low-quality evidence from qualitative research studies and the experience and opinion of the GDG]

4. Short-term treatment of menopausal symptoms:

4.1. Vasomotor symptoms:

- Prescribe HRT only after discussing the short-term (≤5 years) and long-term benefits and risks [box], offering:
  - estrogen and progestins for women with the uterus; and
  - estrogen only in women without the uterus;
  [based on low to moderate quality evidence from network meta-analysis and economic analysis and the experience and opinion of the GDG]
- do not routinely prescribe SSRIs, SNRIs, or clonidine for first-line treatment of vasomotor symptoms only; and
  [based on low to moderate quality evidence from network meta-analysis and economic analysis and the experience and opinion of the GDG]
- Explain that there is some evidence that isoflavones and Cimicifuga racemosa extracts are effective in improving vasomotor symptoms; in any case, explain that:
  - Preparations vary; and
  - The safety of the different preparations is uncertain and interactions with other drugs have been reported;
  [based on low to moderate quality evidence from network meta-analysis and economic analysis and the experience and opinion of the GDG]

4.2. psychological symptoms:

- Consider HRT to improve postmenopausal mood;
  [based on very low to moderate-quality evidence from RCTs and the experience and opinion of the GDG]
- consider cognitive behavioral therapy (CBT) to improve mood or anxiety related to menopause; and
  [based on moderate quality evidence from RCTs and the experience and opinion of the GDG]
- ensure women and healthcare professionals are aware that the evidence does not support the use of SSRIs or SNRIs to improve mood in menopausal women [197];
  [based on low to moderate quality evidence from RCTs and the experience and opinion of the GDG]

4.3. urogenital atrophy:

- Prescribe vaginal estrogen for women with urogenital atrophy (including those taking systemic HRT) and continue treatment as needed to relieve symptoms;
  [based on very low to moderate quality evidence from RCTs and the experience and opinion of the GDG]
- Explain to women with vaginal dryness that moisturizers and lubricants can be used alone or in combination with vaginal estrogen; and

[based on the experience and opinion of the GDG]

- Do not prescribe routine monitoring of endometrial thickness during treatment of urogenital atrophy;
  [based on very low-quality evidence from RCTs and the experience and opinion of the GDG]

4.4. unregulated preparations:

- Explain to women that the efficacy and safety of unregulated biologically identical hormone compounds are unknown;
  [based on the experience and opinion of the GDG]

4.5. Reassessment of therapy:

- Explain to non-hysterectomized women that unexpected vaginal bleeding during the first 3 months of HRT treatment is a frequent side effect, to be reported at the first 3-month follow-up visit; conversely, if bleeding occurs after the first 3 months it should be reported immediately; and
  [based on the experience and opinion of the GDG]
- Explain to women that tapering or stopping HRT will not change symptoms in the long term, but tapering may limit flare-ups in the short term;
  [based on very low to low-quality evidence from RCTs and the experience and opinion of the GDG]

5. women with breast cancer or at high risk (e.g., breast cancer gene [BRCA] carriers) [198-200]:

- HRT is contraindicated in women with a history of hormone-sensitive malignancies, such as breast cancer; and
  [The GDG has not reviewed the evidence on the effects of HRT in this group because it is contraindicated]
- For women at high risk for breast cancer, provide:
  - information on available treatment options (and possible drug interactions such as that between tamoxifen and St. John's wort);
  - information on the need to avoid the SSRIs paroxetine and fluoxetine in case of tamoxifen treatment; and
  - specialist assessment by a professional expert in the management of menopause [201];
  [based on the experience and opinion of the GDG]

6. Long-term benefits and risks of HRT [box]:

6.1 VTE:

- Explain that HRT:
  - Orally increases the risk of VTE; and
  - Transdermally at standard therapeutic doses does not increase the risk of VTE; and
  [based on very low to moderate quality evidence from randomized and observational studies and the experience and opinion of the GDG]
- consider transdermal versus oral HRT in menopausal women at high risk for VTE, including those with BMI >30;
  [based on very low to moderate quality evidence from randomized and observational studies and the experience and opinion of the GDG]

6.2 CVD:

- Explain that HRT:

- does not increase cardiovascular risk if started before age 60 years (the impact of initiating HRT after age 65 years is beyond the scope of this guideline);
- does not affect the risk of death from CVD;
- may be considered for women with cardiovascular risk factors if adequately managed; and
- orally (but not transdermally) is associated with a slightly increased risk of heart attack;

6.3 Type 2 diabetes:

- Explain that HRT (oral or transdermal) is not associated with an increased risk of developing type 2 diabetes and has no adverse effects on glycemic control;
  [based on very low to low-quality evidence from an RCT, observational studies, and the experience and opinion of the GDG]

6.4 breast cancer

- Explain that:
  - estrogen alone is associated with little or no increase in breast cancer risk;
  - estrogen and progestins may be associated with an increased risk of breast cancer; and
  - Any increased risk of breast cancer occurs only during HRT use and is at baseline in the general population at the time of discontinuation of therapy;

  [based on very low to moderate quality evidence from randomized and observational studies and the experience and opinion of the GDG]

6.5 osteoporosis:

- Explain that:
  - The risk of osteoporotic fractures is reduced during HRT;
  - The benefit decreases after stopping treatment; and
  - The benefit may continue longer (after stopping treatment) in women who have taken HRT for a long time (>10 years);

  [based on very low to moderate quality evidence from randomized and observational studies and the experience and opinion of the GDG]

6.6 Dementia:

- explain that there is no evidence that HRT affects the risk of dementia;
  [based on very low to low-quality evidence from an RCT, observational studies, and the experience and opinion of the GDG]

7. POI:

- Taking into account personal history (e.g., previous pharmacological or surgical treatments) and family history, diagnose POI in women <40 years of age based on:
  - menopausal symptoms, including amenorrhea or oligomenorrhea; and
  - increase in FSH levels in two blood assays 6 weeks apart;

  [based on very low to low-quality evidence from observational studies and the experience and opinion of the GDG]
- do not routinely measure AMH to diagnose POI;
  [based on very low to low-quality evidence from observational studies and the experience and opinion of the GDG]
- allow a choice between HRT and combined hormonal contraceptives unless contraindicated (e.g., in women with hormone-sensitive malignancy) up to the age of physiological menopause; and

[based on very low to low-quality evidence from an RCT and the experience and opinion of the GDG]

- consider referral to an experienced specialist to help manage all psycho-physical aspects of this condition;
  [based on the experience and opinion of the GDG]

8. Potential barriers to implementation:
   - Around 1 million women in the UK use treatments for menopausal symptoms [202]; and
   - The advice on the different therapeutic options and forms of support are variable and are based on studies that have been analyzed in this guideline resulting in a review of the recommendations; and
9. Recommendations for future research:
   - In women treated for breast cancer, the safety and efficacy of alternatives to systemic HRT as a treatment for menopausal symptoms;
   - in women previously diagnosed with breast cancer, the impact of systemic HRT on the risk of cancer recurrence, mortality, or aggressiveness;
   - the difference in the risk of menopausal breast cancer between HRT vs. progesterone, progestins, or SERMs;
   - How does HRT affect the risk of VTE;
   - the impact of estradiol and LNG medicated intrauterine devices (IUD) on the risk of breast cancer and VTE;
   - the effects of early use of HRT on the risk of dementia; and
   - the main clinical manifestations of POI and the most common therapeutic interventions' short- and long-term impact [203, 204].

Box. Benefits and risks of HRT started before the age of 65 years to treat menopausal symptoms*:

a) Benefits:
   - improvement of vasomotor, musculoskeletal, depressive symptoms, and sexual difficulties (systemic HRT);
   - improvement of urogenital symptoms (topical or systemic HRT); and
   - prevention of osteoporosis (systemic HRT); in women not taking HRT, the absolute risk of osteoporotic fracture is 69/1000 in 3.5 years; in those using HRT, the risk of fracture is 23 fewer women out of 1000 (95% confidence interval [CI]: -10 to -33); this benefit is maintained during treatment and diminishes upon discontinuation;

b) risks:
   - Unexpected vaginal bleeding: common side effect during the first 3 months; to be reported to the physician if it occurs after the first 3 months;
     [based on the experience and opinion of the GDG]
   - VTE: The absolute risk is 12.4/1000 at 5 years in women not taking HRT; in those taking oral HRT, an additional 10 (95% CI 6-14) in 1000 would be at risk; transdermal HRT is not associated with an increased risk of VTE;
   - stroke: slight increase in risk in women who take estrogen orally, but not in those who take it transdermally; and
   - Breast cancer: The absolute risk is 22.5/1000 at 7.5 years in women not taking HRT; in those taking estrogen + progestins, 5 more women (95% CI -4 to 36) per 1000 are at risk; in those using estrogen alone, 4 fewer women (95% CI -11 to 8) in every 1000 are at risk; the

increased risk of breast cancer when taking both estrogen and progestins disappears when HRT is stopped; and

c) No change in risk:

CHD: There is no increased risk in women treated with HRT compared to those not.*The impact of HRT initiated after the age of 65 years is outside the scope of the guideline.

7. Conclusions

"Menopause" is the term used to indicate the period of a woman's life in which menstruation ceases. It is a physiological phase of aging, characterized by a progressive reduction in the production of female hormones that have contributed to regulating the menstrual cycle for decades. Although the disturbances caused by menopause cannot be defined as real pathologies, they are nevertheless able to significantly affect the quality of life of the woman in menopause, especially if very accentuated; we refer for example to:

- vaginal disorders related to dryness of the mucous membranes;
- pain and discomfort during intercourse;
- vasomotor disorders such as night sweats and hot flushes; and
- sleep disorders.
- Other problems could be associated with menopause, such as osteoporosis and depression.

The symptoms in the most serious cases can be treated by administering HRT, a pharmacological treatment that can also protect against the risk of osteoporosis. However, HRT is also associated with several health risks, as it can increase the risk of developing:

- breast cancer;
- heart disease; and
- stroke.

Some types of therapy have a higher risk, as do some patients, whose probability of developing vascular events and cancer varies according to clinical history, lifestyle, family history, and others. When a physician decides to prescribe HRT, he usually has:

- carefully weighed benefits and risks;
- prescribed the lowest possible dose capable of producing the desired effect; and
- prescribed a therapy for the shortest possible time.

Some HRTs are riskier than others, but for each woman, the individual risk is specific, and associated with medical history and lifestyle. Therefore, it is essential to discuss with the physician the risks and benefits. Any HRT will be carried out with the lowest effective dose and for the shortest possible time. The possible continuation of the therapy should be checked every 3-6 months.

HRT is contraindicated in women with:

- still more or less regular menstruation;
- history of some types of cancer;
- previous strokes, heart attacks, or other episodes of thrombosis;
- presence of cardiovascular risk factors such as hypertension, hypertriglyceridemia, and hypercholesterolemia; and
- liver disease.

The available evidence and the main international agencies, including the European Medicines Agency (EMA), recommend HRT to women who have disorders attributable to menopause, such as

hot flushes and sweating and consequent sleep problems, perceived as important, long-lasting, and responsible for a deterioration in quality of life. Given the available evidence, HRT in menopause is not recommended to prevent health problems that may occur later in life such as CVD or osteoporosis. Assessing the benefits and harms, in general HRT should be reserved:

- to women who entered menopause at less than 45 years of age, i.e. early menopause;
- women who suffer from hot flushes, sweating, and night awakenings in menopause, perceived as important and long-lasting and
- women who negatively experience menopause, and wish to take the therapy after receiving information from the physician on treatment benefits and harms.

Before starting HRT, the woman should talk to her general practitioner (GP) or gynecologist to get information about the discomforts attributable to menopause, HRT benefits and harms, and the fact that once therapy is stopped, the discomforts can return.

The two main hormones used in HRT are estrogen and progestins produced in the laboratory and analogous to the natural hormones produced by the ovaries during reproductive life. HRT may involve taking both hormones (combined HRT) or estrogen alone. Most women take combined HRT because estrogen alone increases the risk of developing uterine cancer. Taking progestins along with estrogen reduces this risk. For this reason, estrogen-only HRT is only recommended for women who have had their uterus removed (hysterectomy). HRT can be used cyclically by taking an appropriate estrogen dosage each day and progestins only during the last 14 days of the month or continuously by taking both estrogen and progestins each day without interruption. It may take a few weeks to feel the positive effects of therapy. Some undesirable effects may appear at the beginning which generally tend to subside spontaneously after the first few weeks of treatment. The main side effects associated with taking estrogen and/or progestins include:

- swelling;
- increased sensitivity of the breasts;
- nausea;
- leg cramps;
- headache or migraines;
- mood swings;
- difficulty in digestion; and
- vaginal bleeding.

Taking medications with meals can help reduce nausea and digestive difficulties, and regular physical exercise can help reduce swelling and leg cramps. HRT can be taken in the form of pills, patches, or gels and each woman must decide together with her physician the most convenient method for her, evaluating the pros and cons of each possibility. Usually taken once a day, tablets are one of the most common ways to take HRT. Tablets are available that contain only estrogen or estrogen and progestins. It is important to know that the risk of venous thrombosis increases slightly with taking medicines by mouth compared to the other modalities. Skin patches are the most used modality, and must be replaced periodically according to the different dosages. Patches are available that release estrogen-only or both estrogen and progestins. Some women find the patches more convenient than taking tablets daily, and they are associated with a slightly lower risk of venous thrombosis than with oral therapy. The estrogen-containing gel is applied to the skin once a day and allows for immediate absorption of the drug. It offers the same advantages as the patch and is especially recommended for women with uteruses removed. Creams, ovules, or vaginal gels

containing only estrogen are an effective and safe solution in case of genital discomfort such as itching, vaginal dryness, pain during sexual intercourse, or recurring urinary tract infections (UTI). This local therapy does not involve the risks described for general replacement therapy because the absorption of hormones by the vaginal route is minimal. For this reason, all women must be informed about this safe and effective treatment opportunity to control disorders (symptoms) related to vaginal dryness that usually appear a few years after the onset of menopause. The optimal duration of treatment with HRT is not certain. However, guidelines recommend prescribing the minimum active dosage for the shortest possible treatment period with periodic assessments of the complaints and the woman's willingness to continue therapy.

As with all drug therapies, the benefits of HRT must be balanced against the risks. They include:

- increased risk of stroke;
- increased risk of venous thrombosis; and
- increased risk of breast cancer, about the duration of therapy.

The increase in risk of these diseases at the individual level is low and the decision whether or not to undertake HRT must be based on an assessment of the individual risk also considering the possible presence of other risk factors for the same diseases. Some more recent studies and the new guidelines of the American NIH and the English NICE state that the overall risk for young women who start HRT early for the treatment of menopause is generally very low. Studies looking at whether HRT can increase the risk of breast cancer have estimated an increase of 1 in 1000 women taking it each year. The risk is lower for women who use estrogen-only therapy than those who take combined estrogen and progestin. After 5 years from the suspension of therapy, the risk seems to return to that of the general population. Therefore, women taking HRT should regularly participate in breast cancer screening. Studies on the role of HRT in increasing the risk of ovarian cancer have given conflicting results. A recent study found that for every 1,000 menopausal women who take HRT, one more case of this cancer occurs for five years. As with breast cancer, the risk decreases once the patient stops taking HRT. Studies examining whether HRT can increase the risk of endometrium cancer have shown an increased likelihood of women taking only estrogen. For this reason, estrogen-only therapy should only be used by women who no longer have a uterus (following a hysterectomy). Combined HRT (estrogen and progestins) reduces this risk almost completely. The studies investigating whether HRT can increase the risk of venous thrombosis have estimated an increase of 2 cases for every 1000 menopausal women each year. Using patches or gels decreases the risk of thrombosis compared to giving HRT by mouth. Studies on the role of HRT in increasing the risk of stroke have estimated an increase of 1 case per 1000 women per year. New studies suggest that starting treatment before age 60 reduces the risk of heart disease.

To control the disturbances (symptoms) of menopause alternative therapies are available, recommended above all for those who cannot or do not want to take hormone-based HRT. Some alternative approaches include:

- tibolone (Livial®), a drug similar to HRT, but characterized by some limitations;
- antidepressants: Some antidepressants can help with hot flushes and night sweats;
- phytoestrogens, such as soy; and
- lifestyle changes, aimed at reducing the extent of the disorders and counteracting their appearance (physical activity, healthy and varied diet, reduction in coffee, alcohol, and spicy foods, quitting smoking, and losing weight if necessary).

Tibolone is a drug that acts like combined HRT (estrogen and progestins). The physician must prescribe it and is usually taken as one tablet daily. It can help relieve ailments such as hot flashes, mood swings, and reduced sex drive, although some studies have suggested it may not be as effective as combined HRT. It is indicated for women who have had their last menstrual cycle more than a year before (postmenopause). The risks of tibolone are similar to those of HRT and include a small increased risk of developing breast cancer and stroke.

Bioidentical or natural hormones are hormonal preparations extracted from plant sources (phytoestrogens). They are similar to human hormones. Many claim that these hormones are a natural and safer alternative to the preparations used in HRT. However, robust scientific evidence on efficacy and safety is unavailable for these preparations. Complementary therapies include various products for treating menopausal disorders (symptoms). They are sold in herbal shops and para-pharmacies. They include herbal remedies such as primrose oil, black cohosh (the root of a South American plant), angelica, ginseng, and St. John's wort. Evidence suggests that some of these remedies, including black cohosh and St. John's wort, can help reduce hot flushes However, in general, scientific evidence does not support many complementary therapies. The quality, purity, and ingredients cannot always be guaranteed and may cause undesirable effects (side effects). It is advisable to seek advice from the family physician, gynecologist, or pharmacist if one is considering complementary therapy.

Lifestyle changes can help reduce some menopausal discomforts without posing any health risks. An appropriate diet is recommended that includes a variety of fruits, vegetables, and cereals, limiting the intake of saturated fats, oils, and sugars. It is advisable to carry out regular physical activity which helps reduce hot flushes, sweats, and urinary incontinence, and improves mood and sleep quality, and is useful in the prevention and treatment of high blood pressure (hypertension) and excess of blood lipids. Smoking increases the risk of heart disease, stroke, osteoporosis, cancer, and several other health problems, and increasing hot flushes. In menopause, therefore, it is advisable to stop smoking or, in any case, try to reduce the number of cigarettes as much as possible. Against hot flushes it is advisable to dress in layers to be able to lighten up if necessary, drink a glass of cold water, move quickly to a cooler environment, and try to identify and avoid the things that trigger hot flushes such as hot drinks, caffeine, spicy foods, alcohol, and stress. Against insomnia it is important to avoid caffeine, which can make it difficult to sleep, and not to drink too much alcohol. It is good practice to be careful not to exercise before bedtime. If sleep is disturbed by hot flushes, it may help to lighten the blankets or shower before sleeping.

Against vaginal discomfort it is possible to use local therapy with estrogen-based creams, ovules, or gels and/or over-the-counter drugs such as water-based vaginal lubricants or moisturizing creams. Products that contain glycerin should be avoided as they can cause burning or irritation in women sensitive to such substances. Staying sexually active helps by increasing blood flow to the vagina. Against urinary incontinence, pelvic floor muscles can be strengthened with simple and effective physical exercises that must always be performed under competent guidance (such as a physiotherapist or a professional nurse) and tend to strengthen the pelvic floor [205-213].

Author Contributions

The authors contributed equally to this work.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Santoro NF, Cooper AR. Primary ovarian insufficiency: A clinical guide to early menopause. 1st ed. New York: Springer; 2016.
2. Anderson DM, Elliot MA, Keith J, Novak PD. Mosby's medical, nursing, & allied health dictionary. 6th ed. St. Louis, MO: Mosby; 2002.
3. Morrison JH, Brinton RD, Schmidt PJ, Gore AC. Estrogen, menopause, and the aging brain: How basic neuroscience can inform hormone therapy in women. J Neurosci. 2006; 26: 10332-10348.
4. Banner EA. Ipma annals from the 60th interstate postgraduate medical assembly. Postgrad Med. 1976; 59: 174-178.
5. Pescetto G, De Cecco L, Pecorari D, Ragni N. Ginecologia e Ostetricia. 5th ed. Rome: Società Editrice Universo; 2017.
6. McKinlay SM. The normal menopause transition: An overview. Maturitas. 1996; 23: 137-145.
7. Sherman B, Wallace R, Bean J, Schlabaugh L. Relationship of body weight to menarcheal and menopausal age: Implications for breast cancer risk. J Clin Endocrinol Metab. 1981; 52: 488-493.
8. Sabia S, Fournier A, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F. Risk factors for onset of menopausal symptoms: Results from a large cohort study. Maturitas. 2008; 60: 108-121.
9. Lee MS, Kim JH, Park MS, Yang J, Ko YH, Ko SD, et al. Factors influencing the severity of menopause symptoms in Korean post-menopausal women. J Korean Med Sci. 2010; 25: 758-765.
10. Carter AE, Merriam S. Menopause. Med Clin North Am. 2023; 107: 199-212.
11. Zanoio L, Barcellona E, Zacchè G. Ginecologia e ostetricia. 2nd ed. Milan: Edra-Masson; 2013.
12. Seifer DB, Naftolin F. Moving toward an earlier and better understanding of perimenopause. Fertil Steril. 1998; 69: 387-388.
13. Cooper R, Mishra G, Clennell S, Guralnik J, Kuh D. Menopausal status and physical performance in midlife: Findings from a British birth cohort study. Menopause. 2008; 15: 1079-1085.
14. Paramsothy P, Harlow SD, Nan B, Greendale GA, Santoro N, Crawford SL, et al. Duration of the menopausal transition is longer in women with young age at onset: The multiethnic Study of Women's Health Across the Nation. Menopause. 2017; 24: 142-149.
15. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Consensus statement: Executive summary of the stages of reproductive aging workshop+ 10: Addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab. 2012; 97: 1159-1168.
16. Huang Y, Wu M, Wu C, Zhu Q, Wu T, Zhu X, et al. Effect of hysterectomy on ovarian function: A systematic review and meta-analysis. J Ovarian Res. 2023; 16: 35.
17. Speroff L, Glass RH, Kase NG. Clinical gynecologic endocrinology and infertility. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 1999.
18. Walker ML, Herndon JG. Menopause in nonhuman primates? Biol Reprod. 2008; 79: 398-406.
19. McAuliffe K, Whitehead H. Eusociality, menopause and information in matrilineal whales. Trends Ecol Evol. 2005; 20: 650.
20. Mason AS. The menopause: The events of the menopause. R Soc Health J. 1976; 96: 70-71.
21. Dalton K. A clinician's view. R Soc Health J. 1976; 96: 75-77.

22. Bartuska DG. Physiology of aging: Metabolic changes during the climacteric and menopausal periods. Clin Obstet Gynecol. 1977; 20: 105-112.
23. Burger HG, Hale GE, Dennerstein L, Robertson DM. Cycle and hormone changes during perimenopause: The key role of ovarian function. Menopause. 2008; 15: 603-612.
24. Te Velde ER, Pearson PL. The variability of female reproductive ageing. Hum Reprod Update. 2002; 8: 141-154.
25. Bottiglioni F, De Aloysio D, Altieri P. Considerazioni fisiopatologiche nel climaterio femminile. Osteoporosi. Il punto di vista del ginecologo. Rome: CIC Edizioni Internazionali; 1994.
26. Bushnell CD, Kapral MK. Stroke in women and unique risk factors. Stroke. 2023; 54: 587-590.
27. Ballinger CB. Mental health aspects. R Soc Health J. 1976; 96: 78-85.
28. Man L, Lustgarten Guahmich N, Vyas N, Tsai S, Arazi L, Lilienthal D, et al. Ovarian reserve disorders, can we prevent them? A review. Int J Mol Sci. 2022; 23: 15426.
29. D'Ignazio T, Grand'Maison S, Bérubé L, Forcillo J, Pacheco C. Hypertension across a Woman's lifespan. Maturitas. 2023; 168: 84-91.
30. da Silva JS, Montagnoli TL, de Sá MP, Zapata-Sudo G. Heart failure in menopause: Treatment and new approaches. Int J Mol Sci. 2022; 23: 15140.
31. Nordin BE. Clinical significance and pathogenesis of osteoporosis. Br Med J. 1971; 1: 571-576.
32. Lee E, Anselmo M, Tahsin CT, Vanden Noven M, Stokes W, Carter JR, et al. Vasomotor symptoms of menopause, autonomic dysfunction, and cardiovascular disease. Am J Physiol Heart Circ Physiol. 2022; 323: H1270-H1280.
33. Shuster LT, Rhodes DJ, Gostout BS, Grossardt BR, Rocca WA. Premature menopause or early menopause: Long-term health consequences. Maturitas. 2010; 65: 161-166.
34. Eden KJ, Wylie KR. Quality of sexual life and menopause. Womens Health. 2009; 5: 385-396.
35. Jones GF. Physiology and management of the climacteric. Calif Med. 1949; 71: 345-348.
36. Lindsay R, Anderson JB. Radiological determination of changes in bone mineral content. Radiography. 1978; 44: 21-26.
37. Barr W. Problems related to postmenopausal women. S Afr Med J. 1975; 49: 437-439.
38. Maki PM, Jaff NG. Brain fog in menopause: A health-care professional's guide for decision-making and counseling on cognition. Climacteric. 2022; 25: 570-578.
39. Haufe A, Baker FC, Leeners B. The role of ovarian hormones in the pathophysiology of perimenopausal sleep disturbances: A systematic review. Sleep Med Rev. 2022; 66: 101710.
40. Avis NE, Crawford SL, Greendale G, Bromberger JT, Everson-Rose SA, Gold EB, et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med. 2015; 175: 531-539.
41. Cox S, Nasseri R, Rubin RS, Santiago-Lastra Y. Genitourinary syndrome of menopause. Med Clin North Am. 2023; 107: 357-369.
42. Brown AD. Postmenopausal urinary problems. Clin Obstet Gynaecol. 1977; 4: 181-206.
43. Grassini E, Benfatti M, Nervi S, Amoruso P, Capetta P. Confronto tra quadro isteroscopico ed istologico in donne con "abnormal uterine bleeding" in pre- e post-menopausa. G Ital di Ostet e Ginecol. 1993; 11: 819.
44. Kasperska-Zajac A, Brzoza Z, Rogala B. Sex hormones and urticaria. J Dermatol Sci. 2008; 52: 79-86.
45. Kronenberg F. Hot flashes: Epidemiology and physiology. Ann N Y Acad Sci. 1990; 592: 52-86.

46. Kronenberg F. Menopausal hot flashes: A review of physiology and biosociocultural perspective on methods of assessment. J Nutr. 2010; 140: 1380S-1385S.
47. Bolaños R, Del Castillo A, Francia J. Soy isoflavones versus placebo in the treatment of climacteric vasomotor symptoms: Systematic review and meta-analysis. Menopause. 2010; 17: 660-666.
48. Bastian LA, Smith CM, Nanda K. Is this woman perimenopausal? JAMA. 2003; 289: 895-902.
49. Barnard RM, Kronenberg F, Downey JA. Effect of fever on menopausal hot flashes. Maturitas. 1992; 14: 181-188.
50. Ohayon MM. Severe hot flashes are associated with chronic insomnia. Arch Intern Med. 2006; 166: 1262-1268.
51. Danesino V, Bolis PF, Nencioni T. Menopausa. Milan: Masson; 1996.
52. Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB, Hollander L. Hormones and menopausal status as predictors of depression in women in transition to menopause. Arch Gen Psychiatry. 2004; 61: 62-70.
53. Santoro N, Brown JR, Adel T, Skurnick JH. Characterization of reproductive hormonal dynamics in the perimenopause. J Clin Endocrinol Metab. 1996; 81: 1495-1501.
54. Pae CU, Mandelli L, Kim TS, Han C, Masand PS, Marks DM, et al. Effectiveness of antidepressant treatments in pre-menopausal versus post-menopausal women: A pilot study on differential effects of sex hormones on antidepressant effects. Biomed Pharmacother. 2009; 63: 228-235.
55. Glazer G, Zeller R, Delumba L, Kalinyak C, Hobfoll S, Winchell J, et al. The Ohio midlife women's study. Health Care Women Int. 2002; 23: 612-630.
56. Kaufert PA, Gilbert P, Tate R. The Manitoba project: A re-examination of the link between menopause and depression. Maturitas. 1992; 14: 143-155.
57. Brown WJ, Mishra GD, Dobson A. Changes in physical symptoms during the menopause transition. Int J Behav Med. 2002; 9: 53-67.
58. Dennerstein L, Dudley EC, Hopper JL, Guthrie JR, Burger HG. A prospective population-based study of menopausal symptoms. Obstet Gynecol. 2000; 96: 351-358.
59. Kravitz HM, Ganz PA, Bromberger J, Powell LH, Sutton-Tyrrell K, Meyer PM. Sleep difficulty in women at midlife: A community survey of sleep and the menopausal transition. Menopause. 2003; 10: 19-28.
60. Verde L, Barrea L, Vetrani C, Frias-Toral E, Chapela SP, Jayawardena R, et al. Chronotype and sleep quality in obesity: How do they change after menopause? Curr Obes Rep. 2022; 11: 254-262.
61. Giardina S, Michelotti A, Zavattini G, Finzi S, Ghisalberti C, Marzatico F. Efficacy study in vitro: Assessment of the properties of resveratrol and resveratrol + N-acetyl-cysteine on proliferation and inhibition of collagen activity. Minerva Ginecol. 2010; 62: 195-201.
62. Ashraf M, Kamp E, Musbahi E, DeGiovanni C. Menopause, skin and common dermatoses. Part 4: Oral disorders. Clin Exp Dermatol. 2022; 47: 2130-2135.
63. Aslan E, Beji NK, Gungor I, Kadioglu A, Dikencik BK. Prevalence and risk factors for low sexual function in women: A study of 1,009 women in an outpatient clinic of a university hospital in Istanbul. J Sex Med. 2008; 5: 2044-2052.
64. Peeyananjarassri K, Liabsuetrakul T, Soonthornpun K, Choobun T, Manopsilp P. Sexual functioning in postmenopausal women not taking hormone therapy in the Gynecological and

Menopause Clinic, Songklanagarind Hospital measured by female sexual function index questionnaire. J Med Assoc Thai. 2008; 91: 625-632.
65. Research Laboratories Merck. The Merck manual of diagnosis and therapy. 5th ed. Milan: Springer-Verlag; 2007.
66. Quattrocchi T, Micali E, Gentile A, La Ferrera EG, Barbaro L, Ciarcià S, et al. Effects of a phyto complex on well-being of climacteric women. J Obstet Gynaecol Res. 2015; 41: 1093-1098.
67. Parmley TH, Woodruff JD. Complete vaginal occlusion in postmenopausal women. Obstet Gynecol. 1975; 46: 235-238.
68. Hickey M, Davis SR, Sturdee DW. Treatment of menopausal symptoms: What shall we do now? Lancet. 2005; 366: 409-421.
69. Migneco A, Ojetti V, Covino M, Mettimano M, Montebelli MR, Leone A, et al. Increased blood pressure variability in menopause. Eur Rev Med Pharmacol Sci. 2008; 12: 89-95.
70. Avioli LV. Senile and postmenopausal osteoporosis. Adv Intern Med. 1976; 21: 391-415.
71. Wylie CM. Hospitalization for fractures and bone loss in adults. Why do we regard these phenomena as dull? Public Health Rep. 1977; 92: 33-38.
72. Gopinath V. Osteoporosis. Med Clin North Am. 2023; 107: 213-225.
73. Gordan GS. Postmenopausal osteoporosis: Cause, prevention and treatment. Clin Obstet Gynaecol. 1977; 4: 169-179.
74. Mesalić L, Tupković E, Kendić S, Balić D. Correlation between hormonal and lipid status in women in menopause. Bosn J Basic Med Sci. 2008; 8: 188-192.
75. Song HK, Grab JD, O'Brien SM, Welke KF, Edwards F, Ungerleider RM. Gender differences in mortality after mitral valve operation: Evidence for higher mortality in perimenopausal women. Ann Thorac Surg. 2008; 85: 2040-2044.
76. Jones S, McNeil M, Koczo A. Updates in cardiovascular disease prevention, diagnosis, and treatment in women. Med Clin North Am. 2023; 107: 285-298.
77. Schneider HP, Heinemann LA, Rosemeier HP, Potthoff P, Behre HM. The Menopause Rating Scale (MRS): Reliability of scores of menopausal complaints. Climacteric. 2000; 3: 59-64.
78. Potthoff P, Heinemann LA, Schneider HP, Rosemeier HP, Hauser GA. The Menopause Rating Scale (MRS II): Methodological standardization in the German population. Zentralbl Gynakol. 2000; 122: 280-286.
79. Heinemann LA, DoMinh T, Strelow F, Gerbsch S, Schnitker J, Schneider HP. The Menopause Rating Scale (MRS) as outcome measure for hormone treatment? A validation study. Health Qual Life Outcomes. 2004; 2: 67.
80. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 141: Management of menopausal symptoms. Obstet Gynecol. 2014; 123: 202-216.
81. Madsen TE, Sobel T, Negash S, Shrout Allen T, Stefanick ML, Manson JE, et al. A review of hormone and non-hormonal therapy options for the treatment of menopause. Int J Womens Health. 2023; 15: 825-836.
82. Crandall CJ, Mehta JM, Manson JE. Management of menopausal symptoms: A review. JAMA. 2023; 329: 405-420.
83. Ye L, Knox B, Hickey M. Management of menopause symptoms and quality of life during the menopause transition. Endocrinol Metab Clin North Am. 2022; 51: 817-836.
84. Woods NF, Mitchell ES. Symptoms during the perimenopause: Prevalence, severity, trajectory, and significance in women's lives. Am J Med. 2005; 118: 14-24.

85. Carpenter J, Gass ML, Maki PM, Newton KM, Pinkerton JV, Taylor M, et al. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. Menopause. 2015; 22: 1155-1174.
86. Thurston RC, Ewing LJ, Low CA, Christie AJ, Levine MD. Behavioral weight loss for the management of menopausal hot flashes: A pilot study. Menopause. 2015; 22: 59-65.
87. Bailey TG, Cable NT, Aziz N, Dobson R, Sprung VS, Low DA, et al. Exercise training reduces the frequency of menopausal hot flushes by improving thermoregulatory control. Menopause. 2016; 23: 708-718.
88. Fausto DY, Leitão AE, Silveira J, Martins JB, Dominski FH, Guimarães AC. An umbrella systematic review of the effect of physical exercise on mental health of women in menopause. Menopause. 2023; 30: 225-234.
89. Witkowski S, Evard R, Rickson JJ, White Q, Sievert LL. Physical activity and exercise for hot flashes: Trigger or treatment? Menopause. 2023; 30: 218-224.
90. Sá KMM, da Silva GR, Martins UK, Colovati ME, Crizol GR, Riera R, et al. Resistance training for postmenopausal women: Systematic review and meta-analysis. Menopause. 2023; 30: 108-116.
91. Liu T, Chen S, Mielke GI, McCarthy AL, Bailey TG. Effects of exercise on vasomotor symptoms in menopausal women: A systematic review and meta-analysis. Climacteric. 2022; 25: 552-561.
92. Avis NE, Legault C, Coeytaux RR, Pian-Smith M, Shifren JL, Chen W, et al. A randomized, controlled pilot study of acupuncture treatment for menopausal hot flashes. Menopause. 2008; 15: 1070-1078.
93. Ross M. A psychosomatic approach to the climacteric. Calif Med. 1951; 74: 240-242.
94. Zhou T. Estimation of placebo effect in randomized placebo-controlled trials for moderate or severe vasomotor symptoms: A meta-analysis. Menopause. 2023; 30: 5-10.
95. Hagey AR, Warren MP. Role of exercise and nutrition in menopause. Clin Obstet Gynecol. 2008; 51: 627-641.
96. Samat A, Rahim A, Barnett A. Pharmacotherapy for obesity in menopausal women. Menopause Int. 2008; 14: 57-62.
97. Yelland S, Steenson S, Creedon A, Stanner S. The role of diet in managing menopausal symptoms: A narrative review. Nutr Bull. 2023; 48: 43-65.
98. Grigolon RB, Ceolin G, Deng Y, Bambokian A, Koning E, Fabe J, et al. Effects of nutritional interventions on the severity of depressive and anxiety symptoms of women in the menopausal transition and menopause: A systematic review, meta-analysis, and meta-regression. Menopause. 2023; 30: 95-107.
99. Schüssler P, Kluge M, Yassouridis A, Dresler M, Held K, Zihl J, et al. Progesterone reduces wakefulness in sleep EEG and has no effect on cognition in healthy postmenopausal women. Psychoneuroendocrinology. 2008; 33: 1124-1131.
100. Lindsay R. Prevention and treatment of osteoporosis. Lancet. 1993; 341: 801-805.
101. O'Connell MB. Prescription drug therapies for prevention and treatment of postmenopausal osteoporosis. J Manag Care Pharm. 2006; 12: S10-S19.
102. Danesino V. Valutazione della profilassi con calcitonina nell'osteoporosi post-menopausale. Rome: CIC Edizioni Internazionali; 1988.
103. McPhee C, Aninye IO, Horan L. Recommendations for improving women's bone health throughout the lifespan. J Womens Health. 2022; 31: 1671-1676.

104. Thangavel P, Puga-Olguín A, Rodríguez-Landa JF, Zepeda RC. Genistein as potential therapeutic candidate for menopausal symptoms and other related diseases. Molecules. 2019; 24: 3892.
105. Simoncini T, Garibaldi S, Fu XD, Pisaneschi S, Begliuomini S, Baldacci C, et al. Effects of phytoestrogens derived from red clover on atherogenic adhesion molecules in human endothelial cells. Menopause. 2008; 15: 542-550.
106. Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T, Cummings SR. Phytoestrogen supplements for the treatment of hot flashes: The Isoflavone Clover Extract (ICE) Study: A randomized controlled trial. JAMA. 2003; 290: 207-214.
107. Cassidy A, Albertazzi P, Lise Nielsen I, Hall W, Williamson G, Tetens I, et al. Critical review of health effects of soyabean phyto-oestrogens in post-menopausal women. Proc Nutr Soc. 2006; 65: 76-92.
108. Johnson A, Roberts L, Elkins G. Complementary and alternative medicine for menopause. J Evid Based Integr Med. 2019; 24: 2515690X19829380.
109. Molla MD, Hidalgo-Mora JJ, Soteras MG. Phytotherapy as alternative to hormone replacement therapy. Front Biosci (Schol Ed). 2011; 3: 191-204.
110. Hooper L, Ryder JJ, Kurzer MS, Lampe JW, Messina MJ, Phipps WR, et al. Effects of soy protein and isoflavones on circulating hormone concentrations in pre- and post-menopausal women: A systematic review and meta-analysis. Hum Reprod Update. 2009; 15: 423-440.
111. Barnes S, Kim H. Cautions and research needs identified at the equol, soy, and menopause research leadership conference. J Nutr. 2010; 140: 1390S-1394S.
112. Aso T. Equol improves menopausal symptoms in Japanese women. J Nutr. 2010; 140: 1386S-1389S.
113. Stahl W, Sies H. Antioxidant defense: Vitamins E and C and carotenoids. Diabetes. 1997; 46: S14-S18.
114. Feduniw S, Korczyńska L, Górski K, Zgliczyńska M, Bączkowska M, Byrczak M, et al. The effect of vitamin E supplementation in postmenopausal women-a systematic review. Nutrients. 2022; 15: 160.
115. Kerr MD, Vaughn C. Psychohormonal treatment during the menopause. Am Fam Physician. 1975; 11: 99-103.
116. Rahimzadeh P, Imani F, Nafissi N, Ebrahimi B, Faiz SH. Comparison of the effects of stellate ganglion block and paroxetine on hot flashes and sleep disturbance in breast cancer survivors. Cancer Manag Res. 2018; 10: 4831-4837.
117. Prague JK, Roberts RE, Comninos AN, Clarke S, Jayasena CN, Nash Z, et al. Neurokinin 3 receptor antagonism as a novel treatment for menopausal hot flushes: A phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2017; 389: 1809-1820.
118. Szeliga A, Podfigurna A, Bala G, Meczekalski B. Kisspeptin and neurokinin B analogs use in gynecological endocrinology: Where do we stand? J Endocrinol Invest. 2020; 43: 555-561.
119. Pan M, Zhou J, Pan X, Wang J, Qi Q, Wang L. Drugs for the treatment of postmenopausal symptoms: Hormonal and non-hormonal therapy. Life Sci. 2023; 312: 121255.
120. Stuursma A, Lanjouw L, Idema DL, de Bock GH, Mourits MJ. Surgical menopause and bilateral oophorectomy: Effect of estrogen-progesterone and testosterone replacement therapy on psychological well-being and sexual functioning; a systematic literature review. J Sex Med. 2022; 19: 1778-1789.
121. Estrogens and the menopausal patient. Med Lett Drugs Ther. 1973; 15: 6-8.

122. Petrucco O. Contraception in the over 40 age group. Aust Fam Physician. 1977; Suppl: 4-7.
123. Estrogen therapy: The dangerous road to Shangri-La. Consum Rep. 1976; 41: 642-645.
124. Sarto GE. Risks and benefits of postmenopausal exogenous estrogen. Int J Gynaecol Obstet. 1977; 15: 189-192.
125. Burger HG. Oestrogen replacement – A boon or a curse? Aust Fam Physician. 1977; 6: 99-104.
126. Ziaei S, Moghasemi M, Faghihzadeh S. Comparative effects of conventional hormone replacement therapy and tibolone on climacteric symptoms and sexual dysfunction in postmenopausal women. Climacteric. 2010; 13: 147-156.
127. Salvatore S, Benini V, Ruffolo AF, Degliuomini RS, Redaelli A, Casiraghi A, et al. Current challenges in the pharmacological management of genitourinary syndrome of menopause. Expert Opin Pharmacother. 2023; 24: 23-28.
128. Yen SS. Estrogen and the menopause. Am Fam Physician. 1977; 16: 87-91.
129. Nemirovsky A, Villela NA, Yuan JC, Patil R, Malik RD. Vaginal hormone therapy for conditions of the lower urinary tract. Curr Urol Rep. 2023; 24: 41-50.
130. Seller JC. Estrogens for the menopause. Maximizing benefits, minimizing risks. Postgrad Med. 1977; 62: 73-79.
131. Mack TM. Uterine cancer and estrogen therapy. Front Horm Res. 1977; 5: 104-116.
132. Berger GS, Fowler Jr WC. Exogenous estrogens and endometrial carcinoma: Review and comments for the clinician. J Reprod Med. 1977; 18: 177-180.
133. Utian WH. Oestrogen therapy and endometrial cancer. Br Med J. 1977; 2: 577-578.
134. Whitehead MI, McQueen J, Minardi J, Campbell S. Clinical considerations in the management of the menopause: The endometrium. Postgrad Med J. 1978; 54: 69-73.
135. Kulkarni J. Estrogen – A key neurosteroid in the understanding and treatment of mental illness in women. Psychiatry Res. 2023; 319: 114991.
136. Shoemaker ES, Forney JP, MacDonald PC. Estrogen treatment of postmenopausal women. Benefits and risks. JAMA. 1977; 238: 1524-1530.
137. Stampfer MJ, Grodstein F, Bechtel S. Postmenopausal estrogen and cardiovascular disease. Contemp Intern Med. 1994; 6: 47-56.
138. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002; 288: 321-333.
139. Roddick Jr JW. Use of estrogens in the climacteric and postmenopausal years. Clin Obstet Gynecol. 1977; 20: 903-911.
140. Speroff L. Postmenopausal hormone therapy and the risk of breast cancer. Maturitas. 1999; 32: 123-129.
141. Donkin R, Fung YL, Singh I. Fibrinogen, coagulation, and ageing. Subcell Biochem. 2023; 102: 313-342.
142. Greenblatt RB, Stoddard LD. The estrogen-cancer controversy. J Am Geriatr Soc. 1978; 26: 1-8.
143. Hammond DO. Cytological assessment of climacteric patients. Clin Obstet Gynaecol. 1977; 4: 49-70.
144. Wiseman RA. Future research – Potentially rewarding areas for investigation. Postgrad Med J. 1978; 54: 95-99.
145. North American Menopause Society. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017; 24: 728-753.

146. Tice LF. Estrogens: Their function, uses and hazards. Part 2. Am Pharm. 1978; 18: 30-33.
147. Detre T, Hayashi TT, Archer DF. Management of the menopause. Ann Intern Med. 1978; 88: 373-378.
148. Longcope C. Hormones: Beneficial or dangerous to the aged? J Am Geriatr Soc. 1978; 26: 145-148.
149. Donohoe F, O'Meara Y, Roberts A, Comerford L, Kelly CM, Walshe JM, et al. Using menopausal hormone therapy after a cancer diagnosis in Ireland. Ir J Med Sci. 2023; 192: 45-55.
150. Borisova AM, Tankova TS, Kamenova P, Dakovska L, Kirilov G, Genov N, et al. Cyproterone acetate improves beta-cell function in postmenopausal women with diabetes mellitus type 2. Akush Ginekol. 2003; 42: 8-14.
151. Bergeron C, Fox H. Low incidence of endometrial hyperplasia with acceptable bleeding patterns in women taking sequential hormone replacement therapy with dydrogesterone. Gynecol Endocrinol. 2000; 14: 275-281.
152. Djerassi C, Miramontes L, Rosenkranz G, Sondheimer F, Longo LD, Steroids LI. Synthesis of 19-nor-17alpha-ethynyltestosterone and 19-nor-17alpha-methyltestosterone. 1954. Am J Obstet Gynecol. 2006; 194: 289.
153. Pinkerton JV, Pickar JH, Racketa J, Mirkin S. Bazedoxifene/conjugated estrogens for menopausal symptom treatment and osteoporosis prevention. Climacteric. 2012; 15: 411-418.
154. Faubion SS, Kingsberg SA, Clark AL, Kaunitz AM, Spadt SK, Larkin LC, et al. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. Menopause. 2020; 27: 976-992.
155. Faubion SS, Larkin LC, Stuenkel CA, Bachmann GA, Chism LA, Kagan R, et al. Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: Consensus recommendations from The North American Menopause Society and The International Society for the Study of Women's Sexual Health. Menopause. 2018; 25: 596-608.
156. Kearley-Shiers K, Holloway D, Janice Rymer, Bruce D. Intravaginal dehydroepiandrosterone for genitourinary symptoms of the menopause: Is the evidence sufficient? Post Reprod Health. 2022; 28: 237-243.
157. Labrie F, Archer DF, Koltun W, Vachon A, Young D, Frenette L, et al. Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. Menopause. 2018; 25: 1339-1353.
158. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. JAMA. 2004; 291: 1701-1712.
159. Kaunitz AM, Women's Health Initiative. Use of combination hormone replacement therapy in light of recent data from the Women's Health Initiative. Medscape Womens Health. 2002; 7: 8.
160. McKay Hart D, Lindsay R, Purdie D. Vascular complications of long-term oestrogen therapy. Front Horm Res. 1977; 5: 174-191.
161. Morris G, Talaulikar V. Hormone replacement therapy in women with history of thrombosis or a thrombophilia. Post Reprod Health. 2023; 29: 33-41.
162. Constantine G, Graham S, Portman DJ, Rosen RC, Kingsberg SA. Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: Results of a randomized, placebo-controlled trial. Climacteric. 2015; 18: 226-232.

163. Kim YJ, Soto M, Branigan GL, Rodgers K, Brinton RD. Association between menopausal hormone therapy and risk of neurodegenerative diseases: Implications for precision hormone therapy. Alzheimers Dement. 2021; 7: e12174.
164. Chlebowski RT, Kuller LH, Prentice RL, Stefanick ML, Manson JE, Gass M, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med. 2009; 360: 573-587.
165. Moyer VA, US Preventive Services Task Force. Menopausal hormone therapy for the primary prevention of chronic conditions: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2013; 158: 47-54.
166. Kreatsoulas C, Anand SS. Menopausal hormone therapy for the primary prevention of chronic conditions. U.S. Preventive Services Task Force recommendation statement. Pol Arch Med Wewn. 2013; 123: 112-117.
167. Nelson HD, Walker M, Zakher B, Mitchell J. Menopausal hormone therapy for the primary prevention of chronic conditions: A systematic review to update the U.S. Preventive Services Task Force recommendations. Ann Intern Med. 2012; 157: 104-113.
168. Utian WH, Gass ML, Sullivan JM, Stettin GD, Gallagher JC, Ettinger B, et al. A decision tree for the use of estrogen replacement therapy or hormone replacement therapy in postmenopausal women: Consensus opinion of The North American Menopause Society. Menopause. 2000; 7: 76-86.
169. Cho L, Kaunitz AM, Faubion SS, Hayes SN, Lau ES, Pristera N, et al. Rethinking menopausal hormone therapy: For whom, what, when, and how long? Circulation. 2023; 147: 597-610.
170. Lundberg G, Wu P, Wenger N. Menopausal hormone therapy: A comprehensive review. Curr Atheroscler Rep. 2020; 22: 33.
171. Pinkerton JV. Hormone therapy for postmenopausal women. N Engl J Med. 2020; 382: 446-455.
172. Johnston SR. Adjuvant systemic therapy for postmenopausal, hormone receptor-positive early breast cancer. Hematol Oncol Clin. 2023; 37: 89-102.
173. Engin-Ustün Y, Ustün Y, Türkçüoğlu I, Mutlu Meydanli M, Kafkasli A, Yetkin G. Short-term effect of tibolone on C-reactive protein in hypertensive postmenopausal women. Arch Gynecol Obstet. 2009; 279: 305-309.
174. Garefalakis M, Hickey M. Role of androgens, progestins and tibolone in the treatment of menopausal symptoms: A review of the clinical evidence. Clin Interv Aging. 2008; 3: 1-8.
175. Vignali M. La veralipride nel trattamento dei sintomi climaterici: Schemi alternativi in terapia ormonale in climaterio, rischi e benefici. Rome: CIC Edizioni Internazionali; 1986.
176. Basly JP, Lavier MC. Dietary phytoestrogens: Potential selective estrogen enzyme modulators? Planta Med. 2005; 71: 287-294.
177. Davis RN. Alternatives to hormone therapy: A clinical guide to menopausal transition. Adv Nurse Pract. 2004; 12: 37-38.
178. Vollmer G, Zierau O. What are phytoestrogens and phyto-SERMS? Pharm Unserer Zeit. 2004; 33: 378-383.
179. Nath A, Sitruk-Ware R. Pharmacology and clinical applications of selective estrogen receptor modulators. Climacteric. 2009; 12: 188-205.
180. Carranza-Lira S, Gooch AL, Saldivar N, Osterwalder MS. Climacteric symptom control after the addition of low-dose esterified conjugated estrogens to raloxifene standard doses. Int J Fertil Womens Med. 2007; 52: 93-96.

181. Adomaityte J, Farooq M, Qayyum R. Effect of raloxifene therapy on venous thromboembolism in postmenopausal women. A meta-analysis. Thromb Haemost. 2008; 99: 338-342.
182. Rosa J, Vanuga P, Payer J, Svobodník A. Raloxifene in clinical practice. Results of the non-interventional study CORAL (COmpliance with RALoxifene). Vnitr Lek. 2008; 54: 217-219.
183. Andersen J, Kamby C, Ejlertsen B, Cold S, Ewertz M, Jacobsen EH, et al. Tamoxifen for one year versus two years versus 6 months of Tamoxifen and 6 months of megestrol acetate: A randomized comparison in postmenopausal patients with high-risk breast cancer (DBCG 89C). Acta Oncol. 2008; 47: 718-724.
184. Sadreddini S, Molaeefard M, Noshad H, Ardalan M, Asadi A. Efficacy of Raloxifen in treatment of fibromyalgia in menopausal women. Eur J Intern Med. 2008; 19: 350-355.
185. Pérez DG, Zahasky KM, Loprinzi CL, Sloan J, Novotny P, Barton D, et al. Tamoxifen-associated hot flashes in women. Support Cancer Ther. 2007; 4: 152-156.
186. Levenson AS, Kliakhandler IL, Svoboda KM, Pease KM, Kaiser SA, Ward III JE, et al. Molecular classification of selective oestrogen receptor modulators on the basis of gene expression profiles of breast cancer cells expressing oestrogen receptor α. Br J Cancer. 2002; 87: 449-456.
187. Arpino G, Nair Krishnan M, Doval Dinesh C, Bardou VJ, Clark GM, Elledge RM. Idoxifene versus tamoxifen: A randomized comparison in postmenopausal patients with metastatic breast cancer. Ann Oncol. 2003; 14: 233-241.
188. Zern TL, Wood RJ, Greene C, West KL, Liu Y, Aggarwal D, et al. Grape polyphenols exert a cardioprotective effect in pre- and postmenopausal women by lowering plasma lipids and reducing oxidative stress. J Nutr. 2005; 135: 1911-1917.
189. Wong RH, Howe PR, Buckley JD, Coates AM, Kunz I, Berry NM. Acute resveratrol supplementation improves flow-mediated dilatation in overweight/obese individuals with mildly elevated blood pressure. Nutr Metab Cardiovasc Dis. 2011; 21: 851-856.
190. Bastianetto S, Dumont Y, Duranton A, Vercauteren F, Breton L, Quirion R. Protective action of resveratrol in human skin: Possible involvement of specific receptor binding sites. PLoS One. 2010; 5: e12935.
191. Johnston SJ, Cheung KL. Fulvestrant – A novel endocrine therapy for breast cancer. Curr Med Chem. 2010; 17: 902-914.
192. Blümel JE, Chedraui P, Baron G, Belzares E, Bencosme A, Calle A, et al. A large multinational study of vasomotor symptom prevalence, duration, and impact on quality of life in middle-aged women. Menopause. 2011; 18: 778-785.
193. Lumsden M. The hormone replacement therapy controversy. BJOG. 2005; 112: 689-691.
194. Krieger N, Löwy I, Aronowitz R, Bigby J, Dickersin K, Garner E, et al. Hormone replacement therapy, cancer, controversies, and women's health: Historical, epidemiological, biological, clinical, and advocacy perspectives. J Epidemiol Community Health. 2005; 59: 740-748.
195. National Institute for Health and Care Excellence. Menopause: Diagnosis and management [Internet]. London: National Institute for Health and Care Excellence; 2019 [cited date 2023 July 30]. Available from: www.nice.org.uk/guidance/ng23.
196. National Institute for Health and Care Excellence. Depression in adults: Treatment and management [Internet]. London: National Institute for Health and Care Excellence; 2022 [cited date 2023 July 30]. Available from: www.nice.org.uk/guidance/ng222.

197. National Institute for Health and Care Excellence. Suspected cancer: Recognition and referral [Internet]. London: National Institute for Health and Care Excellence; 2023 [cited date 2023 August 24]. Available from: www.nice.org.uk/guidance/ng12.
198. National Institute for Health and Care Excellence. Early and locally advanced breast cancer: Diagnosis and management [Internet]. London: National Institute for Health and Care Excellence; 2023 [cited date 2023 July 30]. Available from: www.nice.org.uk/guidance/ng101.
199. National Institute for Health and Care Excellence. Familial breast cancer: Classification, care and managing breast cancer and related risks in people with a family history of breast cancer [Internet]. London: National Institute for Health and Care Excellence; 2019 [cited date 2023 July 30]. Available from: www.nice.org.uk/guidance/cg164.
200. Health and Social Care Information Centre. Prescription cost analysis – England, 2010 [Internet]. Leeds: National Health Service; 2023 [cited date 2023 July 30]. Available from: www.hscic.gov.uk/catalogue/PUB02274.
201. Loizzi V, Dellino M, Cerbone M, Arezzo F, Chiariello G, Lepera A, et al. Hormone replacement therapy in BRCA mutation carriers: How shall we do no harm? Hormones. 2023; 22: 19-23.
202. Chiechi LM, Berardesca C, Lobascio A, Carrieri M, Loizzi P. Postmenopausal users of long-term hormonal replacement therapy: Social-cultural features. Clin Exp Obstet Gynecol. 1999; 26: 88-90.
203. Cartabellotta A, Laganà AS, Zini MC, Triolo O. Linee guida per la diagnosi e il trattamento della menopausa. Evidence. 2016; 8: e1000149.
204. Marsden J. The British menopause society consensus statement on the management of estrogen deficiency symptoms, arthralgia and menopause diagnosis in women with treated for early breast cancer. Post Reprod Health. 2022; 28: 199-210.
205. Moscati A. Una quasi eternità. Milan: Nottetempo; 2006.
206. Barbieri RL. Update in female reproduction: A life-cycle approach. J Clin Endocrinol Metab. 2008; 93: 2439-2446.
207. Simon J, Braunstein G, Nachtigall L, Utian W, Katz M, Miller S, et al. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. J Clin Endocrinol Metab. 2005; 90: 5226-5233.
208. Buster JE, Kingsberg SA, Aguirre O, Brown C, Breaux JG, Buch A, et al. Testosterone patch for low sexual desire in surgically menopausal women: A randomized trial. Obstet Gynecol. 2005; 105: 944-952.
209. Vermeulen A. The hormonal activity of the postmenopausal ovary. J Clin Endocrinol Metab. 1976; 42: 247-253.
210. von Hagens C, Reinhard-Hennch B, Strowitzki T. Alternative therapies for menopausal women. MMW Fortschr Med. 2008; 150: 29-32.
211. Massobrio M, Ardizzoja M, Carmazzi CM. Fisiopatologia clinica e trattamento del climaterio femminile. Torino: Centro Scientifico Editore; 1998.
212. Jugulytė N, Žukienė G, Bartkevičienė D. Emerging use of vaginal laser to treat genitourinary syndrome of menopause for breast cancer survivors: A review. Medicina. 2023; 59: 132.
213. Gullo G, Etrusco A, Cucinella G, Basile G, Fabio M, Perino A, et al. Ovarian tissue cryopreservation and transplantation in menopause: New perspective of therapy in postmenopausal women and the importance of ethical and legal frameworks. Eur Rev Med Pharmacol Sci. 2022; 26: 9107-9116.