A Practitioner's Toolkit for Managing the Menopause

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ABSTRACT

Objective   A number of learned societies, including the International Menopause Society, have produced position statements pertaining to the use of postmenopausal hormone therapy. These documents are highly informative but are not designed for use by primary-care physicians and nurse practitioners during routine consultations. Our aim was to produce a toolkit for practitioners that could be used during office consultations to assist them in the assessment and management of the menopause.

Methods   We used clinical experience in primary care, combined with published diagnostic algorithms, positions statements from learned medical societies and relevant peer-reviewed literature to develop assessment and management algorithms relevant to the primary care of women age 40 years and older.

Results   The resultant 'Practitioner's Toolkit for Managing the Menopause' comprises algorithms for the reasons why a woman might present, determination of menopausal status, key information that should be ascertained, issues that may influence treatment decision-making, hormonal and non-hormonal treatment options, symptom management and patient review, and a brief supporting document.

Conclusions   We believe these algorithms and supporting document provide an accessible desktop tool for health-care practitioners caring for women at midlife. The toolkit has been endorsed by the International Menopause Society for global use.

INTRODUCTION

Several position statements and consensus statements pertaining to postmenopausal hormone therapy and the management of the menopause have been published[1–5]. These have been based on detailed literature reviews and expert opinion, and provide evidence-based clinical practice guidance. However, a simple assessment and decision-making tool for use by primary health-care practitioners is lacking. Therefore our aim was to develop such a tool that started at the point a woman aged 40 years or more walked in the door.

Based on clinical practice experience, our first step was to address the reasons why a woman might present, that is, her symptoms or concerns (Figure 1). We then followed with the menopause staging decision tool (Figure 1), a pragmatic algorithm developed to accommodate women who may have amenorrhea due to hysterectomy, endometrial ablation or hormonal contraception, and settings in which hormonal levels cannot be measured (due to cost or remoteness)[6]. The assessment (Figure 2), treatment options (Figures 3 and 4) and symptom management algorithms (Figures 5 and 6) are derived from the published literature. The included therapies are comprehensive to enable global application, with the caveat that the availability of the included hormonal and non-hormonal treatments, and indications for their use by regulatory bodies, vary between countries.

This manuscript includes the assessment and management algorithms that can be assembled into a folded desktop reference and the brief supporting text. To our knowledge, this is the first clinical practice tool for the management of the menopause in primary care that has international application.

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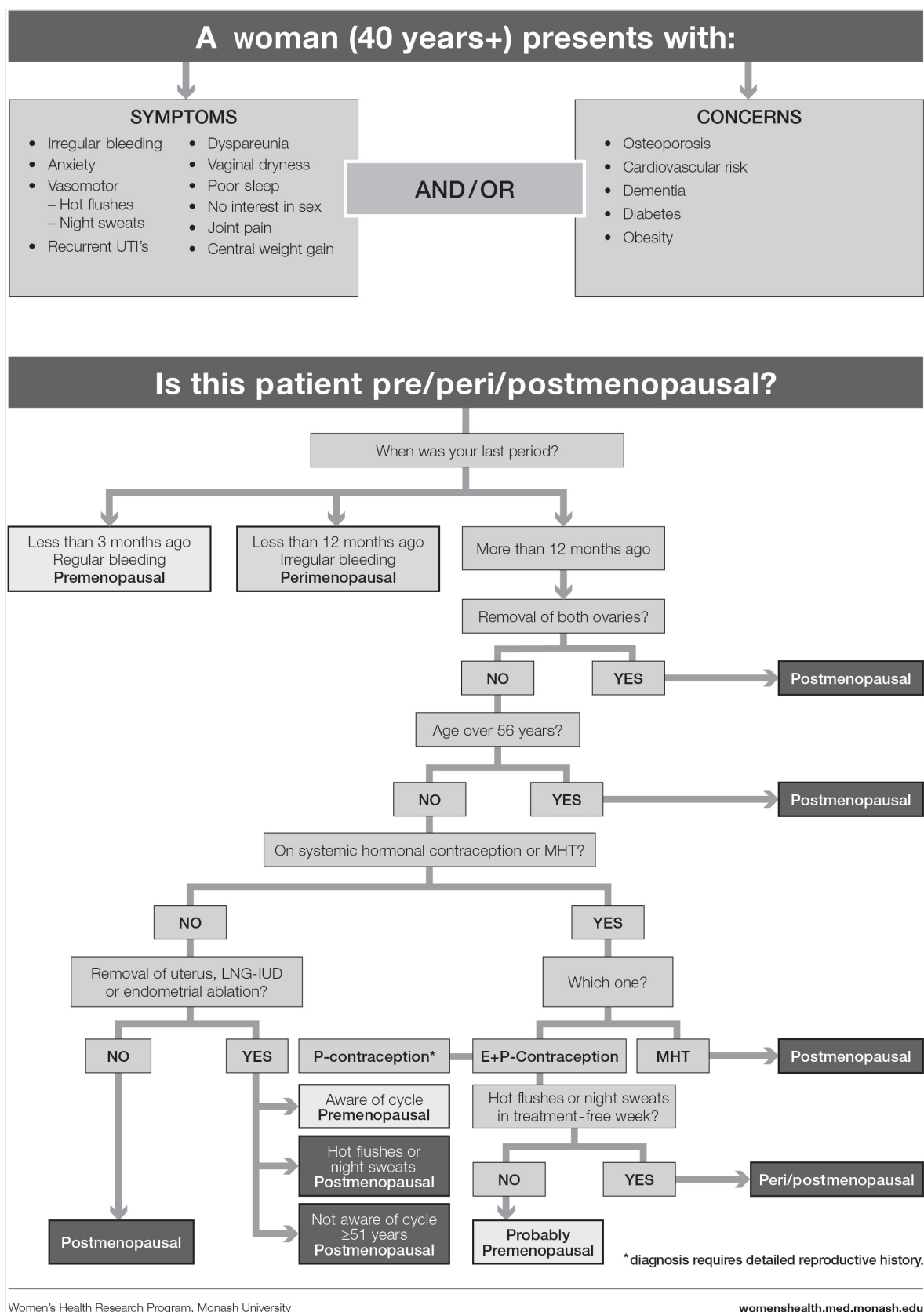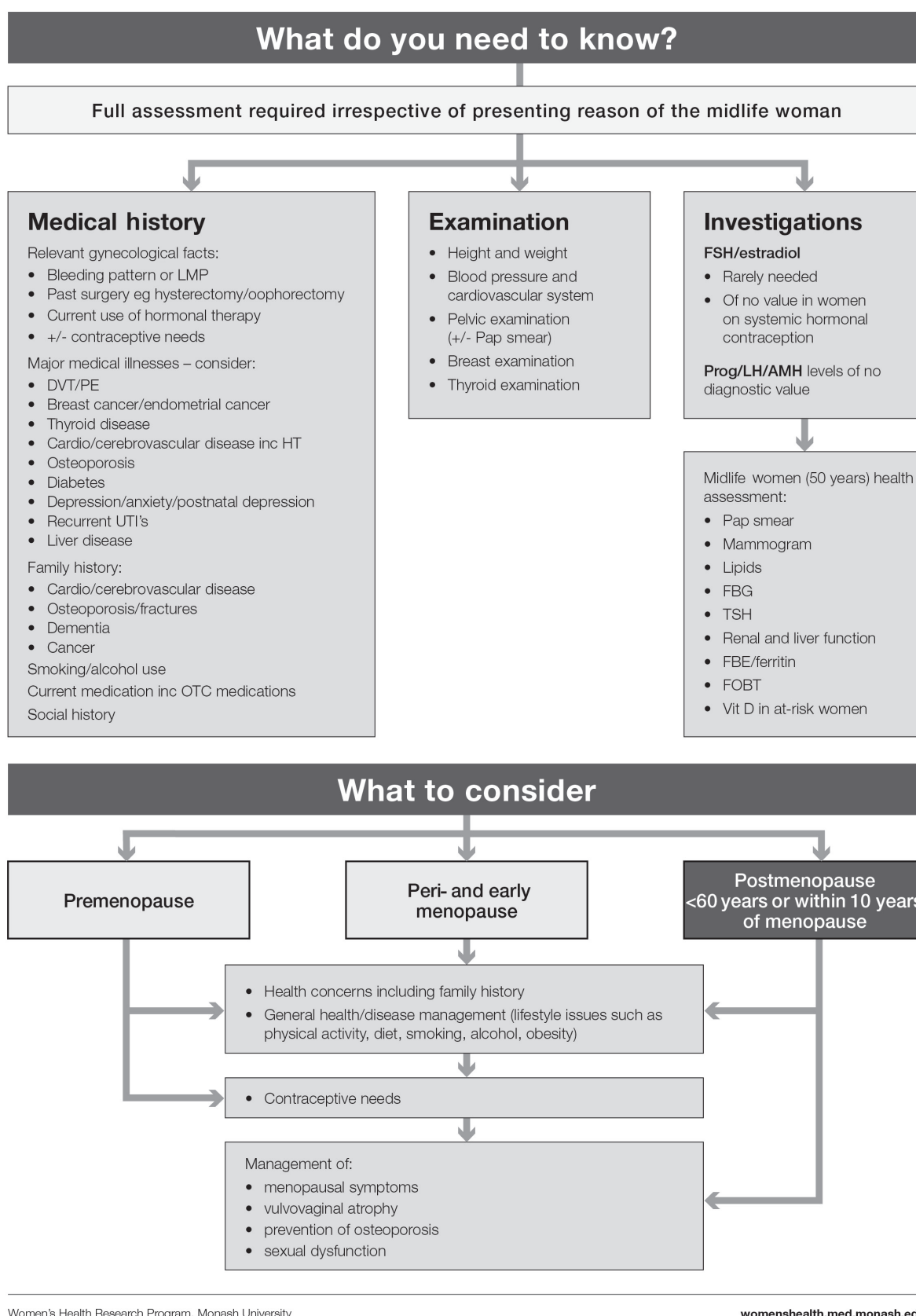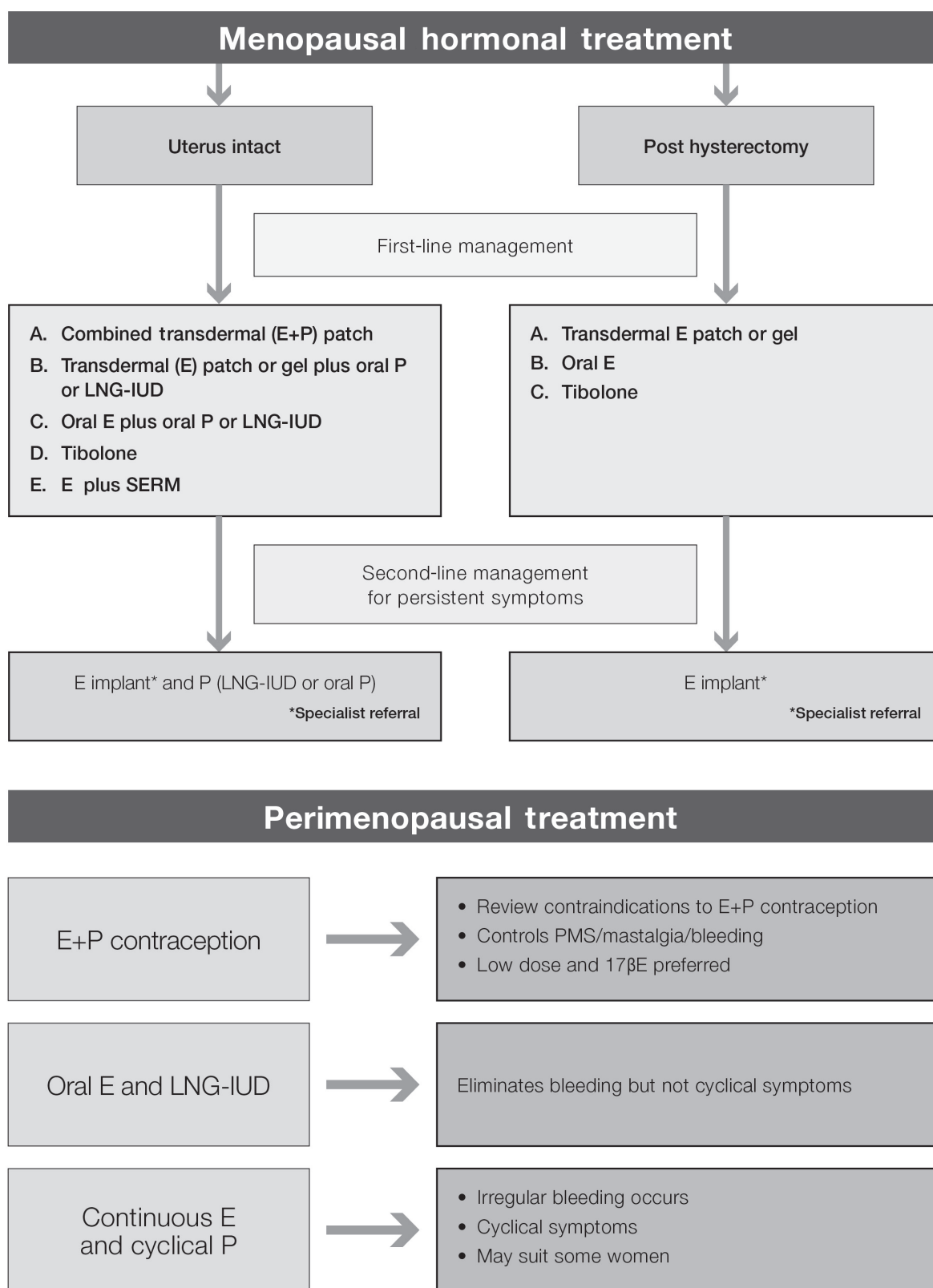
A woman (40 years+) presents with:

SYMPTOMS
- Irregular bleeding
- Anxiety
- Vasomotor
  – Hot flushes
  – Night sweats
- Recurrent UTI's
- Dyspareunia
- Vaginal dryness
- Poor sleep
- No interest in sex
- Joint pain
- Central weight gain

AND/OR

CONCERNS
- Osteoporosis
- Cardiovascular risk
- Dementia
- Diabetes
- Obesity

Is this patient pre/peri/postmenopausal?

When was your last period?

| Less than 3 months ago Regular bleeding **Premenopausal** | Less than 12 months ago Irregular bleeding **Perimenopausal** | More than 12 months ago |

Removal of both ovaries?

NO → Age over 56 years?

YES → **Postmenopausal**

Age over 56 years?

NO → On systemic hormonal contraception or MHT?

YES → **Postmenopausal**

On systemic hormonal contraception or MHT?

NO → Removal of uterus, LNG-IUD or endometrial ablation?

YES → Which one?

Removal of uterus, LNG-IUD or endometrial ablation?

NO → **Postmenopausal**

YES →
- Aware of cycle **Premenopausal**
- Hot flushes or night sweats **Postmenopausal**
- Not aware of cycle ≥51 years **Postmenopausal**

Which one?

- P-contraception*
- E+P-Contraception
- MHT → **Postmenopausal**

P-contraception* →
- Aware of cycle **Premenopausal**
- Hot flushes or night sweats **Postmenopausal**
- Not aware of cycle ≥51 years **Postmenopausal**

E+P-Contraception → Hot flushes or night sweats in treatment-free week?

NO → **Probably Premenopausal**

YES → **Peri/postmenopausal**

*diagnosis requires detailed reproductive history.

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Figure 1

What do you need to know?

Full assessment required irrespective of presenting reason of the midlife woman

Medical history

Relevant gynecological facts:
- Bleeding pattern or LMP
- Past surgery eg hysterectomy/oophorectomy
- Current use of hormonal therapy
- +/- contraceptive needs

Major medical illnesses – consider:
- DVT/PE
- Breast cancer/endometrial cancer
- Thyroid disease
- Cardio/cerebrovascular disease inc HT
- Osteoporosis
- Diabetes
- Depression/anxiety/postnatal depression
- Recurrent UTI's
- Liver disease

Family history:
- Cardio/cerebrovascular disease
- Osteoporosis/fractures
- Dementia
- Cancer

Smoking/alcohol use

Current medication inc OTC medications

Social history

Examination

- Height and weight
- Blood pressure and cardiovascular system
- Pelvic examination (+/- Pap smear)
- Breast examination
- Thyroid examination

Investigations

FSH/estradiol
- Rarely needed
- Of no value in women on systemic hormonal contraception

Prog/LH/AMH levels of no diagnostic value

Midlife women (50 years) health assessment:
- Pap smear
- Mammogram
- Lipids
- FBG
- TSH
- Renal and liver function
- FBE/ferritin
- FOBT
- Vit D in at-risk women

What to consider

Premenopause

Peri- and early menopause

Postmenopause <60 years or within 10 years of menopause

- Health concerns including family history
- General health/disease management (lifestyle issues such as physical activity, diet, smoking, alcohol, obesity)

- Contraceptive needs

Management of:
- menopausal symptoms
- vulvovaginal atrophy
- prevention of osteoporosis
- sexual dysfunction

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Figure 2

Menopausal hormonal treatment

| Uterus intact | Post hysterectomy |

First-line management

Uterus intact

A. Combined transdermal (E+P) patch

B. Transdermal (E) patch or gel plus oral P or LNG-IUD

C. Oral E plus oral P or LNG-IUD

D. Tibolone

E. E plus SERM

Post hysterectomy

A. Transdermal E patch or gel

B. Oral E

C. Tibolone

Second-line management
for persistent symptoms

E implant* and P (LNG-IUD or oral P)
*Specialist referral

E implant*
*Specialist referral

Perimenopausal treatment

| E+P contraception | • Review contraindications to E+P contraception
• Controls PMS/mastalgia/bleeding
• Low dose and 17βE preferred |

| Oral E and LNG-IUD | Eliminates bleeding but not cyclical symptoms |

| Continuous E and cyclical P | • Irregular bleeding occurs
• Cyclical symptoms
• May suit some women |

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Figure 3

MHT dosing[1]

Estrogen

	Low dose	Moderate dose	High dose
CEE	0.3 – 0.45 mg/day	0.625 mg/day	1.25 mg/day
17β-estradiol	0.5 – 1.0 mg/day	1.5 – 2 mg/day	2 mg
Estradiol valerate	0.5 mg/day	1 mg/day	2 mg/day
Transdermal estradiol patch	25 – 37.5 µg/day	50 µg/day	75 – 100 µg/day
Estradiol hemihydrate gel	0.5 mg/day	1.0 mg/day	1.5 mg/day

Sequential P – daily dose for 14 days per month- lowest "safe" dose with:

	Low dose E	Moderate to high dose E
Dydrogesterone	5 mg	10 mg
Micronized progesterone	100 mg	200 mg
MPA	5 mg	5 – 10 mg
Norethisterone acetate (NETA)	1.25 mg	1.25 – 2.5 mg

Continuous P – daily dose – lowest "safe" dose with:

	Low dose E	Moderate to high dose E
Dydrogesterone	5 mg	5 – 10 mg
Drospirenone	0.5 mg	—
Micronized progesterone	100 mg	100 mg
MPA	2.5 mg	2.5 – 5 mg
Norethisterone acetate (NETA)	0.5 – 1.0 mg	>1.0 – 2.5 mg
LNG-IUD	device releasing 20 µg / 24 hours	

Tibolone

Tibolone	2.5 mg daily

Evidence-based non-hormonal treatment[1] for vasomotor symptoms

Estrogen and SERM therapy

CEE 0.45 mg plus bazedoxifene	20 mg daily

SSRI or SSRI/SNRI– low dose (also treats menopausal mood disorder)	Venlafaxine 75mg, desvenlafaxine 50mg, escitalopram 10mg, paroxetine 7.5 mg daily
Clonidine	100 µg daily
Gabapentin	300 – 900 mg daily
Pregabalin	75 – 150 mg twice a day
Hypnosis	
Cognitive behavior therapy	
Weight loss for obese women	
Stellate ganglion blockade*	Severe resistant VMS *specialist referral

[1] – Availability of hormonal/nonhormonal treatment and indications for use from regulatory bodies vary between countries.

Figure 4

Menopausal symptom management

Identify and treat the main issues

- Localized urogenital symptoms
- Moderate to severe menopausal symptoms
- Sexual dysfunction
- Concerns, no symptoms

Exclude dermatological or infective causes

Consider psychosocial causes

Vaginal non-E therapy ±

Vaginal E therapy ±
Consider MHT to prevent bone loss ±

Hormonal treatment

Non-hormonal treatment

Moisturizers Lubricants

17β-estradiol or estriol pessary, ring, cream or tablet

E+P (if uterus intact)
E (if no uterus)
E+bazedoxifene
Tibolone

- SSRI/SNRI
- Clonidine
- Gabapentin
- Hypnosis
- CBT therapy
- Weight loss

Consider tibolone or testosterone therapy

Advice/ information on lifestyle changes, e.g. nutrition/ physical activity for weight control

Women > 60 or 10 years after menopause

Caution

Contraindications

- Estrogen-dependent cancer
- High risk of VTE/DVT or thrombophilia
- Personal wish not to use hormones
- Undiagnosed genital bleeding
- Severe active liver disease
- Untreated hypertension

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Figure 5

Review of treatment

Non-MHT	MHT	Vaginal E therapy

6-8 weeks

NO symptom relief or has side-effects → Change dose OR therapy

Symptom relief

6 months

NO symptom relief or has side-effects → Change dose OR therapy

Symptom relief

6-12 monthly review ← Recurrence of symptoms

Review of:
- Efficacy
- Side-effects
- Risks

Specialist review

Abbreviations

AMH	Anti-Müllerian hormone		**µg**	microgram
β	Beta		**mg**	milligram
CEE	Conjugated equine estrogen		**MPA**	Medroxyprogesterone acetate
DVT	Deep vein thrombosis		**NETA**	Norethisterone acetate
E	Estrogen		**OCP**	Oral contraceptive pill
FBE	Full blood examination		**OTC**	Over the counter
FBG	Deep venous thrombosis		**P**	Progestogen
FOBT	Fecal occult blood test		**Prog**	Progesterone
FSH	Follicle stimulating hormone		**SERM**	Selective estrogen receptor modulator
HT	Hypertension		**SNRI**	Selective noradrenaline reuptake inhibitor
inc	including		**SSRI**	Selective serotonin reuptake inhibitor
LH	Luteinizing hormone		**TSH**	Thyroid stimulating hormone
LMP	Last menstrual period		**UTI**	Urinary tract infection
LNG-IUD	Levonorgestrel intrauterine device		**VMS**	Vasomotor symptoms
MHT	Menopausal hormone therapy		**VTE**	Venous thromboembolism

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Figure 6

A PRACTITIONER'S TOOLKIT FOR MANAGING THE MENOPAUSE

Supporting notes

The menopause is a normal biological event that affects all women. Each woman experiences and views the menopause transition and their postmenopausal years differently. The experience will be influenced by the age at which menopause occurs, why it occurs (surgical versus natural), the health and well-being of the individual, and their ethnicity, environment and culture.

Treatment will be determined by symptom severity, weighing of benefits and risks, and each woman's personal expectations.

DEFINITIONS

Menopause is the permanent cessation of menstruation in a non-hysterectomized woman. As a woman with an intact uterus may have stopped menstruating for a range of reasons, such as having had an endometrial ablation or a hormonal intrauterine device (IUD) inserted, a more pragmatic approach is to define menopause as the permanent cessation of ovarian function.

The average age of natural menopause has been reported as being at 51.5 years in developed countries[7]. In general, it occurs between the ages of 45 and 55 years.

- *The perimenopause* is the time from the onset of cycle irregularity through until 12 months after the menstrual period.
- *Surgical menopause* is the removal of both ovaries.
- *Primary ovarian insufficiency (POI)* is cessation of ovarian function before the age of 40 years.

Factors associated with earlier menopause include hysterectomy, smoking, lower level of education, living at an altitude above 2000 m and being single. Factors that have been associated with a later menopause include parity, higher body mass index (BMI) and oral contraceptive use[7-9].

BASIC PHYSIOLOGY

Menopause occurs because the ovaries run out of eggs. The basic reproductive unit of the ovary is the ovarian follicle. Each ovarian follicle contains a single oocyte. A female infant at birth has approximately 300 000 ovarian follicles. By approximately 37 years of age, this number is depleted to about 25 000, and at menopause few/none remain.

Loss of ovarian follicles is associated with diminished *estradiol* (E2) and ovarian *inhibin* production, and increased production of pituitary follicle stimulating hormone (FSH). Loss of follicles also results in a fall in the production of anti-Müllerian hormone (AMH). AMH is produced by developing ovarian follicles. When follicle numbers decline,

AMH levels fall. Hence, AMH levels decline with age. Measurement of AMH is useful in predicting ovarian response to ovulation induction (low level predicts a poor response).

Changes in FSH, E2, inhibin B and AMH may precede or coincide with the development of menstrual irregularity or symptoms.

The *stages of menopause* have been classified by the Stages of Reproductive Aging Workshop (STRAW), most recently updated as STRAW + 10[10]. Using this guide, the following phases are characterized as follows.

Late reproductive phase

- Changes in menstrual cycle flow/length;
- FSH, E2 variable;
- AMH, inhibin B low;
- Some women develop intermittent symptoms.

Menopause transition (perimenopause)

- Increased cycle variability;
- FSH increased;
- E2 variable;
- AMH, inhibin B low;
- Symptoms more likely.

Postmenopause

- Cessation of menstruation;
- FSH elevated;
- E2, AMH, inhibin B low, progesterone continually low;
- Symptoms much more likely.

Androgens and the menopause

- Androgens are produced by the adrenal cortex and the ovaries. Circulating blood levels of total and free testosterone, dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS) and androstenedione decline with age, with the decline commencing in the late reproductive years[11,12].
- There is no acute change in androgens across the natural menopause[12,13].
- Surgical menopause is associated with a significant reduction in testosterone[12,14] and lower androgens have been reported in women with POI[15,16].

HOW TO DIAGNOSE MENOPAUSE

The diagnosis of menopause is mostly straightforward if a woman is over the age of 45 years and reports cessation of

menstruation for over 12 months, with or without symptoms (Figure 1).

If a woman has had a hysterectomy and has classic menopausal symptoms, treatment can be instituted without a firm diagnosis, as menstrual bleeding is not an issue if estrogen is to be prescribed.

Challenging situations, in terms of diagnosis, include women who have had an endometrial ablation, have a progestin-releasing IUD, are using systemic hormonal contraception (estrogen plus progestin oral, transdermal or vaginal ring or implanted/depot progestin) or have symptoms and are less than 45 years old.

Measurement of hormones, when and why

Most women do not need to have any hormonal tests done to diagnose menopause (Figure 2).

- Progestogen IUD *in situ* – can usually be treated with estrogen if symptomatic without any diagnostic blood tests needed.
- Endometrial ablation – still need to prescribe progestogen protection for the endometrium. It is appropriate to institute treatment if the woman is symptomatic without any hormonal tests.
- For women using systemic hormonal contraception – hormonal tests are completely uninformative as ovarian function is suppressed. The only way to ascertain a woman's menopausal status while using systemic hormonal contraception is to cease usage.

Hormone measurement may be useful for:

- Women with subtle/fluctuating symptoms, for example predominant mood change and few vasomotor symptoms. Of note, a single observation of normal FSH and estradiol does not exclude perimenopause as hormone levels may fluctuate at this time.
- Women younger than 45 years old.

Hormone measurements are required:

- To diagnose POI – diagnosis requires FSH to be elevated and E2 to be low on at least two occasions at least 4–6 weeks apart. Other investigations are usually indicated once POI is diagnosed.

Other biochemical investigations based on clinical assessment

- Exclude other causes of amenorrhea in younger women

  – pregnancy
  – hyperprolactinemia
  – thyroid disease
  – hypothalamic amenorrhea (anorexia nervosa, etc.)
- Exclude other common causes of fatigue, mood change, hotness

  – thyroid disease – thyroid stimulating hormone (TSH)
  – iron deficiency – hemoglobin/iron stores
  – type 2 diabetes – fasting blood glucose
- Consider whether fasting lipids, vitamin D measurement required.

PERIMENOPAUSAL SYMPTOMS

Because hormone levels fluctuate during the perimenopausal years, women might present with symptoms of relative estrogen excess, estrogen deficiency or both. Typical estrogen excess symptoms include breast tenderness, menorrhagia, migraine, nausea, shorter cycle length and a shorter follicular phase[17].

THE SYMPTOMS OF THE MENOPAUSE

There is substantial variability between women in the symptoms that occur due to the hormonal changes at menopause. The symptoms listed below are primarily due to systemic estrogen deficiency and most are alleviated by estrogen therapy. Common symptoms are:

1. Vasomotor symptoms (VMS)
   – hot flushes
   – night sweats
2. Psychological
   – depressive symptoms
   – anxiety/irritability
   – sleep disturbance
   – overall diminished well-being
   – lessened memory
   – lessened concentration
3. General physical
   – sleep disturbance
   – fatigue
   – headaches
   – muscle/joint pains
   – crawling sensations on skin (formication)
4. Urogenital and sexual
   – vaginal itching, burning
   – dryness and dyspareunia
   – urinary frequency, urgency.

Symptom prevalence

It is well established that menopausal symptoms may range from none at all through to debilitating.

VMS are most commonly reported in the late menopause transition and after menopause. VMS are more common in obese women.

Within the US population, symptoms are more common in African-American women than Caucasian women, and less common in Chinese and Japanese women[18].

A UK study reported that:

- 1 in 4 women experience *severe* VMS,
- 1 in 3 experience *severe* psychological symptoms (depression, anxiety),
- 1 in 2 women report *moderate to severe* symptoms of sleep disturbance, joint pain or headache) and,
- at least 1 in 4 women has sexual problems[19,20].

High rates of sleeping difficulty, VMS, joint and muscular discomfort and of vaginal dryness have been reported for women living in urban and remote regions across the globe, dispelling the myth that menopausal symptoms are phenomena of the developed world[21–24].

Symptom duration

There is no age limit at which menopausal symptoms cease. Women who experience severe symptoms, either from early in the menopause transition or from their final menstrual period, continue to experience severe symptoms for several years[19].

At least 10% of women have bothersome VMS 10 years after their menopause has occurred, with as many as 16% of 85-year-olds continuing to experience VMS[25]. Urogenital atrophy due to estrogen deficiency persists unless treated, so effectively all untreated postmenopausal women are affected.

OTHER HEALTH CONSEQUENCES OF THE CHANGE IN HORMONES AT MENOPAUSE

The fall in E2 at menopause has a number of adverse metabolic effects and health effects:

Metabolic

- Central abdominal fat deposition (even in slim women),
- Insulin resistance and increased risk of type 2 diabetes.

Cardiovascular

- Impaired endothelial function (impaired vascular integrity),
- Increased cholesterol (total cholesterol and low density lipoprotein cholesterol).

Skeletal

- Accelerated bone loss,
- Increased fracture risk.

Neurological

- Persistent controversy as to whether the fall in estrogen at menopause and decline in androgens with age adversely affect cognitive performance.

Urogenital

- Atrophic vaginitis,
- Urinary tract – frequency, cystitis, urge incontinence, dysuria.

MANAGEMENT (Figures 3–5)

Considerations for ALL women at menopause

The importance of improving lifestyle factors such as good nutrition, being physically active, cessation of smoking and limiting alcohol should be highlighted, as these can confer benefits to all women. *All women* should be reviewed in terms of:

- Cardiovascular disease risk (blood pressure and lipids),
- Diabetes (fasting blood glucose),
- Urogenital health (consider local hormonal/non-hormonal therapy),
- Cancer screening – breast check, PAP smear, mammogram (recommended frequency varies between countries).

General advice for symptom management

- Dressing in layers, using a small fan, etc. may help women manage VMS, but will not reduce VMS or alleviate other symptoms.
- Weight reduction may result in reduced VMS in overweight women[26].
- The effects of exercise on VMS are mixed[27]; however, increased physical activity may improve sleep and general well-being.

Menopausal hormone therapy

Since publication of the first of the Women's Health Initiative (WHI) hormone studies, the use of menopausal hormone therapy (MHT) has raised concerns. In 2013, several international medical societies formulated a 'Global Consensus Statement on Menopausal Hormone Therapy'[28] which can be found at http://informahealthcare.com/doi/pdf/10.3109/13697137.2013.771520.

This statement was endorsed by the American Society for Reproductive Medicine, the Asia Pacific Menopause Federation, the Endocrine Society, the European Menopause and Andropause Society, the International Menopause Society, the International Osteoporosis Foundation and the North American Menopause Society. Several core recommendations are listed in this document, with the first being:

'MHT is the most effective treatment for vasomotor symptoms associated with menopause at any age, but *benefits are more likely to outweigh risks* for symptomatic women before the age of 60 years or within 10 years after menopause.'

Other documents summarizing the benefits and risk of MHT in detail are accessible[2,3,29]. There is general consensus that:

- Endometrial protection with a progestogen is essential in non-hysterectomized women, whereas hysterectomized women should be prescribed estrogen alone.
- Women with premature ovarian insufficiency should be treated with MHT at least until the age of natural menopause.
- Oral estrogen is associated with an increased risk of venous thromboembolic disease (VTE), although the absolute risk is small for women < 60 years old. The risk appears to be lower/not at all with transdermal estrogen. Therefore transdermal estrogen is preferred for women at increased risk of VTE, i.e. smokers, obese women.
- Breast cancer is a contraindication to the use of MHT.
- The prescription of individually formulated and compounded hormone preparations is not recommended.
- MHT prevents bone loss and fractures in women aged up to 60 years, or within 10 years of menopause.
- Testosterone therapy, given in a dose appropriate for a woman, may improve sexual desire and arousal.
- Oral DHEA is not effective for the treatment of menopausal VMS, mood changes or sexual dysfunction.

Perimenopausal women

Treatment goals are cycle control, contraception and symptom relief.

Oral contraceptive pill

For the perimenopausal woman needing contraception, the combined oral contraceptive pill (OCP) provides contraception, menstrual cycle control, and relief from VMS and other symptoms. It also prevents bone loss and treats acne that can occur at this time. Each woman's risks must be assessed including smoking status, blood pressure, lipid profile, migraine aura history, thrombosis and cardiovascular risk, and family history.

- Low-dose ethinylestradiol OCP (20 μg) or estradiol-containing OCP may be preferred. A 30 μg OCP can probably be used with equal safety (UK Medical Eligibility Criteria for Contraceptive use, http://www.fsrh.org/pdfs/UKMEC2009.pdf). However, some women have VMS when using ethinylestradiol that are alleviated when they are switched to an estradiol-containing OCP.
- VMS in the pill-free week can be managed by eliminating the placebo tablets or adding a low dose of supplemental estrogen.
- In some countries, weekly transdermal, monthly injectable, or monthly intravaginal contraceptive options will provide the same benefits with cyclical bleeding.

- Women can transition from contraceptive hormone therapy to MHT when contraception is no longer required.

Progestogen-only regimens

The levonorgestrel-releasing intrauterine device (LNG-IUD) provides contraception and suppresses the endometrium and is an excellent option for the management of heavy bleeding. Although initial breakthrough bleeding may occur, 80% of women are amenorrheic at 1 year[30]. The LNG-IUD can be combined with oral/transdermal estrogen and can be left *in situ* for 5 years.

High-dose oral progestogen-only regimens (medroxyprogesterone acetate or micronized progesterone) may alleviate hot flushes and treat endometrial hyperplasia. However side-effects (weight gain, mastalgia, fluid retention, vaginal discharge, and dry mouth) can be a problem at these doses. Lower doses can be tried but may be less effective. Short-term use may be applicable in women who do not want to take estrogen. They can be used cyclically for the first 12–14 days of the cycle and produce predictable bleeding in the majority of women.

Cyclical MHT

This can be instituted during the perimenopause, with the progestin dose timed to the first 14 days of a woman's own cycle. However, as the dose of estrogen is not sufficient to suppress ovulation, women often experience symptoms of estrogen excess including mastalgia and erratic bleeding.

Menopausal hormone therapy after menopause

The primary use of MHT (estrogen $\pm$ progestogen therapy) is to alleviate symptoms of the menopause, namely hot flushes, night sweats, sleep disturbance, arthralgia and vaginal dryness and therefore improve the quality of life of women who, without MHT, find these symptoms intolerable.

- For women with an intact uterus, progestogen therapy is taken with estrogen to protect the lining of the uterus from over-stimulation by estrogen.
- This can be continuous estrogen with cyclic progestogen for 14 days out of a monthly cycle, or as continuous combined MHT where both the estrogen and progestogen are taken every day.
- Cyclic MHT results in scheduled menstrual bleeding after the progestogen is ceased.
- Continuous combined MHT results in no bleeding in 90% of women after 12 months. Breakthrough bleeding is not uncommon in the first few months of this type of regimen. If breakthrough bleeding is persistent or prolonged, then investigation of the endometrium is required.
- For women who have undergone a hysterectomy, the administration of estrogen therapy alone is appropriate.

MHT FORMULATIONS (Figure 4)

Estrogen

Estrogen can be used systemically as oral conjugated equine estrogen, estradiol valerate, estrone sulfate or micronized estradiol; transdermal estradiol (patches, gels, spray); a vaginal estradiol ring; and as implanted estradiol pellets. Intranasal estradiol, which is also highly effective, is no longer available. Vaginal estrogen is used exclusively for the treatment of urogenital atrophy.

Oral estrogen preparations

Advantages include:
* Convenience, and
* Reliable absorption for most users.

Disadvantages include:

* Increased risk of VTE disease,
* Increased risk of cholelithiasis,
* Increased sex hormone binding globulin (SHBG), and therefore decreased free testosterone,
* Increased thyroid binding globulin (TBG) – may need to adjust thyroxine dose,
* Administration of higher total dose.

Transdermal estradiol preparations

Advantages include:

* Avoidance of gut and first-pass hepatic metabolism: no change in SHBG or TBG, null effect on hepatic coagulation proteins,
* Little/no increase in VTE disease,
* Lower total dose,
* Convenience for some women (e.g. once- or twice-a-week patch).

Disadvantages include:

* Patches may cause skin irritation and rarely general allergic reaction,
* Gel can be 'sticky' and inconvenient,
* Occasionally poorly absorbed,
* Women may forget to change twice-weekly patch.

Progestogen

Progestogen therapy is required for all women who have not had a hysterectomy. Progestogens include micronized progesterone and the synthetic progestins. There is evidence that supports micronized progesterone as being safer than synthetic progestin therapy in terms of breast cancer and cardiovascular disease risk[31,32].

Micronized progesterone is taken either orally or the same capsule can be used as an intravaginal pessary. Synthetic progestins are mostly taken orally, separately or combined with oral estrogen, or in a combined estradiol–progestin patch.

The LNG-IUD is available in some countries and in appropriate circumstances is an excellent option for progestin effects to be achieved in the endometrium with minimization of systemic side-effects.

Non-prescription progesterone creams are widely available and are being used by many women who believe this treatment will preserve bone, act as an alternative to MHT, may be substituted for synthetic progestins in MHT regimes and will alleviate menstrual and premenstrual symptoms. Some[33,34], but not all studies[35] indicate that, if a sufficient amount of transdermal progesterone can be administered, it may alleviate vasomotor symptoms and afford endometrial protection in the short term, but long-term benefit and safety need to be established.

Managing clinical side-effects of MHT therapy

Common adverse effects of estrogen include nausea, headache and breast tenderness. Combined estrogen–progestogen therapy can result in irregular, and occasionally heavy, bleeding.

Progestin therapy may cause lowered mood or irritability. When this occurs, either the dose needs to be reduced or the patient needs to be switched to another progestin. Micronized progesterone may result in less adverse mood effects.

Initiating treatment with low-dose estrogen will minimize the likelihood of adverse effects. Transdermal estrogen is less likely than oral estrogen to cause nausea. Changing from one estrogen regimen to another in many cases can alleviate certain adverse effects.

All women using systemic MHT require medical review every 6 months. Review should include updating medical history and a routine general health and breast check (Figure 6). Investigations should be individually assessed with at least biannual mammography.

Bone densitometry measurement (DXA) should be performed where indicated[36].

All unexpected vaginal bleeding warrants investigation and, when appropriate, specialist referral. Transvaginal ultrasound and/or endometrial biopsy is required if there is any excessive or prolonged bleeding 3–6 months after commencing MHT.

The need for ongoing MHT, the formulation and dose requirement should be regularly reviewed (Figure 6).

Effectiveness

Estrogen therapy alleviates VMS and the other commonly reported symptoms of the menopause in 96% of women[5]. Low-dose therapy can be highly effective.

Treatment tips

If symptoms persist on high-dose oral therapy, there is no point increasing the dose if SHBG is high, as the administered

estrogen will just be bound by the SHBG. Switch to non-oral.

If symptoms persist on high-dose, non-oral therapy, check serum estradiol to be sure the patient is actually absorbing the administered dose.

Although there is substantial controversy about whether menopause causes depression or major mood disturbance, many women report alleviation of anxiety and improved well-being with the use of estrogen therapy. There is also evidence for improved sleep quality.

OTHER THERAPIES WITH HORMONE-LIKE ACTIONS (Figure 4)

Tibolone

Tibolone is a unique chemical compound that provides an alternative to estrogen–progestin therapy. Tibolone itself has very weak actions. It is metabolized in the gut and target tissues to metabolites that exhibit estrogenic, progestogenic and androgenic actions. Therefore it alleviates VMS, has favorable mood effects, treats urogenital atrophy and does not activate the endometrium – and therefore does not cause vaginal bleeding. Tibolone can also be converted to an active form which has weak androgen action. As a result, women may experience an improvement in sexual interest and responsiveness when they use tibolone[37]. It is uncommon for women using tibolone to experience breast tenderness, and tibolone does not increase mammographic density (unlike standard oral estrogen–progestin therapy). Tibolone prevents bone loss and has been shown to reduce fractures in older women[38].

Tibolone should not be prescribed with other hormone therapy and is contraindicated in women with breast cancer. Tibolone has not been shown to increase the risk of VTE, cardiovascular disease or endometrial cancer.

Occasionally, women report fluid retention and mild weight gain with tibolone. Vaginal bleeding or spotting may occur in women just after commencing tibolone; however, this is uncommon.

Tibolone 1.25 mg/day has been associated with a small increase in the risk of ischemic stroke in older women[38]. For women aged 60–69 years, the risk of stroke was 2.8/1000 person-years for tibolone and 1.0/1000 person-years for placebo. In the same study, the risks for both breast and colon cancer were significantly reduced with tibolone compared with placebo.

Estrogen + selective estrogen receptor modulator

The combination of a selective estrogen receptor modulator (SERM) with estrogen has been described as a tissue-selective estrogen complex (TSEC) therapy. The first of these has now been approved in the USA: the oral combination of conjugated equine estrogen (CEE) 0.45 mg/day with 20 mg of bazedoxifene (BZE). This therapy alleviates VMS, alleviates urogenital atrophy, preserves bone and does not stimulate the endometrium such that vaginal bleeding is minimal[39,40]. Mastalgia is uncommon with this therapy. The incidence of VTE with CEE/BZE needs further clarification. An increase in VTE has been reported in studies of BZE alone[41], but not in studies of combined CEE/BZE[42].

Oral therapy for urogenital atrophy

Ospemifene is a SERM that has been approved in the USA for the treatment of vulvovaginal atrophy in postmenopausal women. The recommended dose is 60 mg/day. Ospemifene has an estrogen-like effect in the vagina (increases superficial cells and decreases parabasal cells and lowers vaginal pH). It results in a small, but statistically significant reduction in dyspareunia[43]. The most common adverse effect of ospemifene is VMS, which has been reported to occur in 10% of treated women[44].

NON-HORMONAL OPTIONS WITH EVIDENCE TO SUPPORT EFFICACY (Figure 4)

An array of non-hormonal therapies are recommended for the treatment of VMS, few of which have evidence to support efficacy.

Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are effective in some, but not all women with VMS, and have the added benefit of improving mood and well-being. Recommended doses are listed in the Toolkit (Figure 4).

A recent systematic review and meta-analysis concluded: 'SSRI use is associated with modest improvement in the severity and frequency of hot flushes but can also be associated with the typical profile of SSRI adverse effects'[45].

Clonidine

Clonidine is sometimes prescribed for the management of VMS for women who cannot take estrogen. Studies of clonidine for VMS have been small and most show no benefit over placebo[46,47]. A dose of 100–150 µg/day may be effective in some women, although the effect is modest[48,49]. The most common side-effect, dry mouth, is dose-related.

Gabapentin

Gabapentin is an anti-epileptic that also is indicated for the treatment of neuropathic pain. It has been found in several studies to reduce VMS in postmenopausal women in doses of

300–900 mg/day[50,51]. The anxiolytic effects of gabapentin may also be beneficial for some women. Side-effects include headache, dizziness and somnolence and are dose-related. Preliminary data also support the off-label use of *pregabalin*, in a dose of 75–150 mg twice daily, for the treatment of VMS[52].

Hypnosis

Hypnosis has been shown to diminish VMS in a study of postmenopausal women[53]. Although this needs further verification, it can be considered as a treatment option for women who are unable to take hormone therapy and who have not achieved a satisfactory outcome with other non-hormonal interventions.

Cognitive behavior therapy

Cognitive behavior therapy (CBT) employs psychotherapeutic behaviour modification to help women deal with VMS. In expert hands, CBT has been shown to significantly reduce VMS[54,55].

Stellate ganglion blockade

Blockade of the stellate ganglion at the anterolateral aspect of the C6 vertebra on the right side under fluoroscopy has been shown to alleviate severe VMS for up to 12 weeks[56]. This option could be considered for women with severe, debilitating VMS when other treatments are contraindicated or ineffective and where expertise in this procedure is available.

ANDROGEN THERAPY

Testosterone

There is no level of testosterone below which a woman can be said to be androgen-deficient, and a 'testosterone deficiency syndrome' has never been biochemically defined[57]. However, several randomized, clinical trials have demonstrated efficacy of testosterone, in doses appropriate for women, for the treatment of low sexual desire/arousal disorder. This has been shown for naturally and surgically menopausal women, and for MHT users and non-users[58–60].

Although a transdermal patch, releasing 300 μg of testosterone per day, was approved for surgically menopausal women in Europe, this treatment was not approved outside EU countries. Presently, it is not available in most countries, including EU countries. Testosterone pellets have been used for the past three decades in Australia and the UK for testosterone therapy for women (recommended dose being one half of a 100 mg testosterone pellet every 6 months or more), but these pellets are no longer available. A transdermal testosterone cream (AndroFeme 1%) can be prescribed in Australia, although it has not been approved by the Australian Therapeutics Goods Administration. The recommended starting dose is 0.5 ml/day, applied to the lower torso/upper thigh. It is essential that testosterone levels are monitored shortly after commencement of treatment and regularly during treatment (6-monthly) as absorption is variable. Blood levels of calculated free testosterone should be kept below the upper limit of the range for premenopausal women.

Women should be advised that, when testosterone is administered in a dose that results in levels within the normal female range, the effects of treatment usually do not emerge for 6–8 weeks. Therefore treatment needs to be continued at least this long as a therapeutic trial. If no benefit is seen by 6 months, treatment should be discontinued.

Side-effects of testosterone therapy are rare when treatment is prescribed for appropriately selected women and given in the appropriate dose. Side-effects from *excessive* dosage can include masculinization with acne and excess body hair, fluid retention and cliteromegaly. These side-effects are rare if the appropriate dose of testosterone is administered.

Women with severe acne or severe excess body hair should not use testosterone. Similarly, women who are pregnant, lactating or who have a suspected cancer should not use testosterone as a standard precaution.

DHEA

DHEA was popularized in the 1990s as a treatment to improve well-being, sexual function and possibly reduce menopausal symptoms. Subsequent randomized, placebo-controlled trials have not shown oral DHEA to be effective as a treatment for estrogen deficiency symptoms in postmenopausal women. It has been shown to be no more effective than placebo for low sexual desire, diminished well-being and cognitive function[61]. Data to support the routine prescription of DHEA to postmenopausal women with adrenal insufficiency are also lacking[62].

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