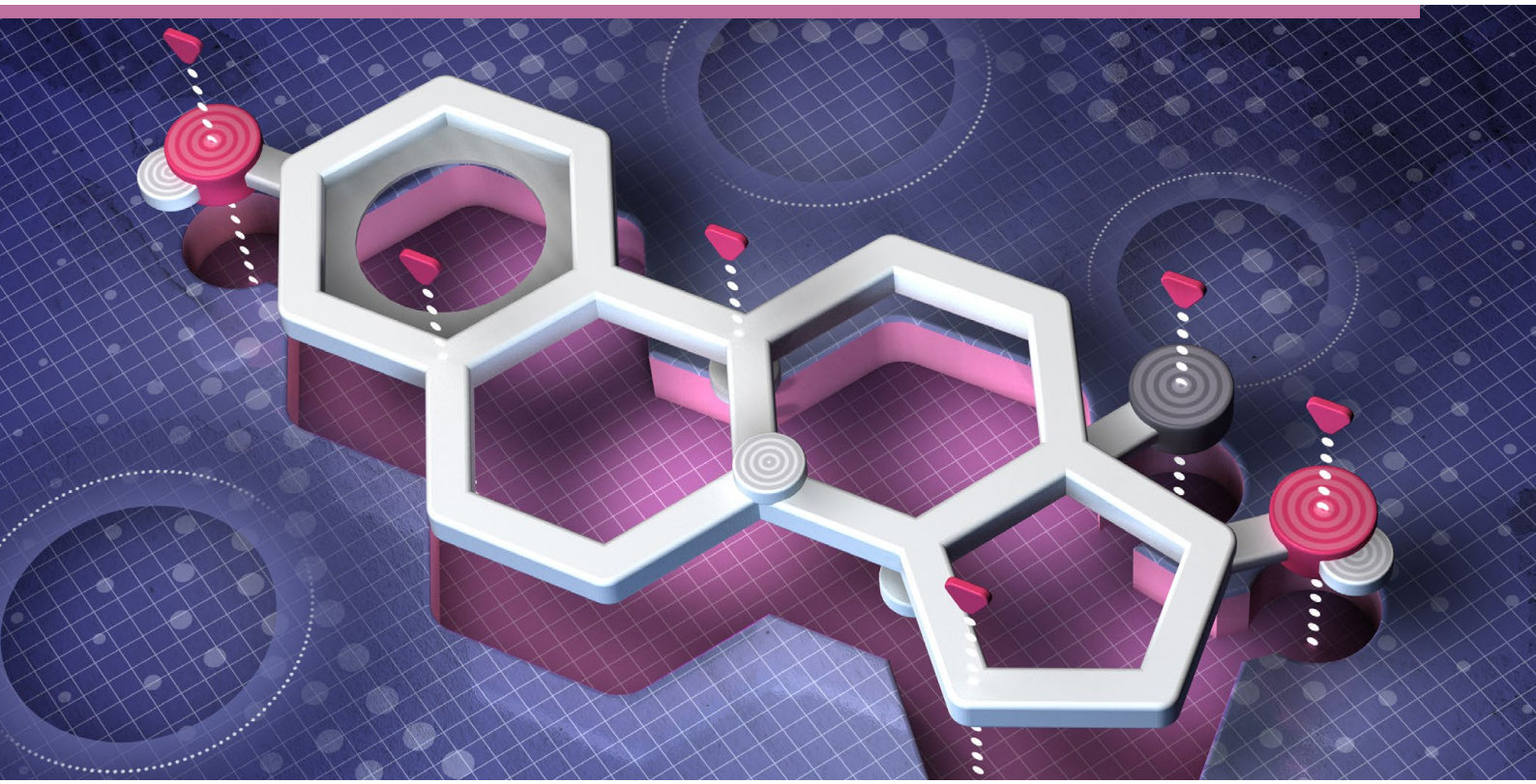

Menopausal hormone therapy: where are we now?

Menopausal hormone therapy (MHT) is an effective treatment for symptoms associated with menopause, such as hot flushes, night sweats, mood changes, sleep disturbances and changes in sexual function. While the evidence around MHT has changed over the years, there is now international consensus that the benefits of MHT are likely to outweigh the risks for most women aged < 60 years or within ten years of menopause, for whom menopausal symptoms are affecting their quality of life.

KEY PRACTICE POINTS:

- Every woman's experience of menopause is different, and perceptions of menopause vary across cultures. Most women will experience some menopause symptoms, however, only some will seek treatment.
- Menopausal hormone therapy (MHT) is likely to offer overall benefit to women with menopausal symptoms affecting their quality of life if they are aged < 60 years or within ten years of menopause
- Adverse outcomes associated with MHT include breast cancer, stroke and venous thromboembolism (VTE). However, the risk of these outcomes depends on factors such as the age or time since menopause when MHT is initiated, MHT type, dose, duration of use,* route of administration, and whether a progestogen is used.
- Women prescribed MHT who have a uterus must take progestogen in addition to oestrogen to avoid an increased risk of endometrial cancer; women who have had a hysterectomy can take oestrogen alone
- Among the oestrogen and progestogen formulations available, transdermal oestrogen (funded) and micronised progesterone (funded) are associated with the lowest risk of adverse effects
- There is no specific recommended duration for MHT. The decision to continue treatment should be reviewed on an annual basis, taking into account any changes in the patient's risk factors, adverse effects and extent of benefit.
- If women primarily seek assistance for urogenital symptoms of menopause, vaginal products are recommended instead of MHT. This includes moisturisers, lubricants or a vaginal oestrogen cream or pessary.

* Stroke and VTE risk do not appear to be affected by duration of treatment, but are influenced by the woman's age.[1]

Menopausal hormone therapy (MHT): still an effective treatment for menopausal symptoms

Menopause is associated with a range of symptoms including hot flushes and night sweats (vasomotor symptoms), vaginal dryness, itching or pain during intercourse, changes in mood or sleep patterns, and joint or musculoskeletal discomfort. Most women close to the age of menopause in New Zealand report they have menopausal symptoms when asked, but little data is available on ethnic or cultural differences or preferred treatment approaches.[2] Many women will not find their symptoms troublesome enough to seek assistance, but some women may experience symptoms which significantly affect their quality of life.

MHT* is the most effective treatment for the vasomotor symptoms and urogenital atrophy associated with menopause.[1] However, MHT use has been controversial, largely due to early research findings from the Women's Health Initiative trials that raised concerns about the safety of this treatment.† Evidence from longer-term follow-ups of these trials, as well as from other RCTs and observational studies, has led to international consensus that the benefits of MHT are likely to outweigh the risks in most women with menopause symptoms affecting their quality of life if they are aged < 60 years or within ten years of menopause.[1, 3, 4]

* Hormone replacement therapy for peri- or postmenopausal women is now referred to as MHT to differentiate it from hormone replacement for other endocrine conditions, e.g. growth hormone replacement.

† The Women's Health Initiative trials investigated whether MHT would reduce the incidence of heart disease, cancer and fractures in postmenopausal women.[5] The trials were stopped early due to increased risks of breast cancer, stroke, coronary heart disease and pulmonary embolism. It should be noted that these trials included few women aged < 60 years or within ten years of menopause with menopausal symptoms (the group that MHT is primarily indicated for), and only one route of administration (oral) and only one formulation and dose of oestrogen and progestogen.[1]

What are the current recommendations for prescribing MHT?

Initiate MHT in women who experience symptoms that affect their quality of life

The primary reason to initiate MHT should be to treat menopause symptoms or replace a hormone deficiency, e.g. due to primary ovarian insufficiency.[1, 3] Some women may experience additional benefits, such as reduced risks of fracture, type 2 diabetes or cardiovascular disease, however, these should not be the primary reason for initiating MHT.[1]

 For information on the use of MHT for women with primary ovarian insufficiency, see:
www.bpac.org.nz/2019/ovarian.aspx

MHT is safest in women closer to the natural age of menopause

The decision to initiate MHT should be guided by the woman's age or the time since her final menstrual period (see: "What do the current data say about the safety of MHT?").[1] The benefit-risk ratio is most favourable for women aged < 60 years or within ten years of menopause, provided they have no contraindications.[1] For women aged > 60 years or more than ten years since menopause, the benefit-risk ratio is less favourable due to the greater absolute risks of stroke, venous thromboembolism and dementia. The overall risk of coronary heart disease is not increased, but there may be some increased risk in women who initiate combined oestrogen + progestogen MHT > 20 years since menopause.[1]

There is no upper limit on the duration of MHT use

The average duration of vasomotor symptoms of menopause is 7.4 years and some women may experience symptoms for more than ten years.[1] Guidelines do not recommend an upper limit to how long women should use MHT; provided new contraindications do not develop, e.g. a new onset hormone-dependent cancer, MHT can be continued if it is beneficial.[1]

Prescribing MHT

The main points to consider when deciding whether to prescribe MHT and what regimen to use include (see Figure 1 for examples):

- The woman's age or time since her final menstrual period
- Any contraindications (see Figure 1) or cautions to MHT use (see below)
- Whether she has an intact uterus; MHT regimens must include oestrogen + progestogen in women with a uterus as oestrogen alone can cause endometrial hyperplasia and increase the risk of endometrial cancer

Caution is recommended when prescribing MHT to women with:[17]

- An increased risk of breast cancer
- A strong family history of venous thromboembolism or inherited thrombophilia – discussion with a haematologist is recommended
- Increased risk of cardiovascular disease or venous thromboembolism (caution with oral oestrogen)
- Hypertriglyceridaemia (> 400 mg/d) (caution with oral oestrogen)

When discussing menopausal symptoms, ensure that women who are sexually active are prescribed an appropriate contraceptive, as this is still required until women are postmenopausal (see: "Contraceptive needs for perimenopausal women").

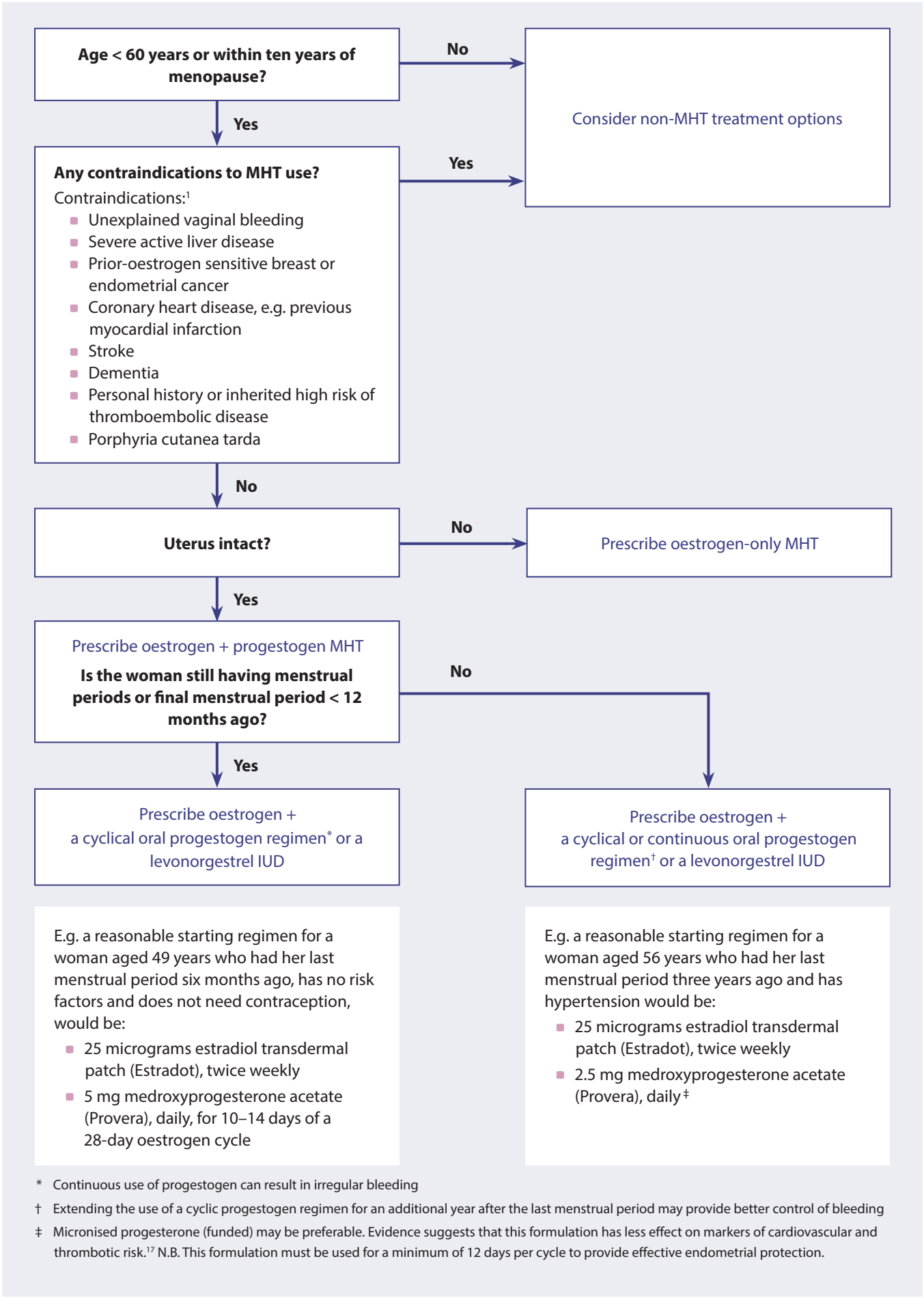

Figure 1. Prescribing algorithm for initiating MHT in women with menopause symptoms affecting their quality of life[1]

What do the current data say about the safety of MHT?

In 2017, the North American Menopause Society (NAMS) released a comprehensive summary of the evidence on the benefits and risks of MHT.[1]* The risks associated with MHT depend on the woman's age or time since menopause, whether oestrogen + progestogen or oestrogen alone is used, the formulation, dose, duration of use,† route of administration, and personal and family risks of breast cancer, cardiovascular disease, stroke and venous thromboembolism.[1]

* The recommendations made by NAMS take into consideration findings from the Women's Health Initiative trials, other RCTs, meta-analyses of RCTs and observational studies. This does not include additional analyses to provide overall risk estimates.

† Stroke and VTE risk do not appear to be affected by duration of treatment, but are influenced by the woman's age.[1]

No differences in all-cause mortality with MHT

An 18-year cumulative follow-up of the Women's Health Initiative trials, which included over 27,000 women, found no difference in all-cause, cardiovascular or total cancer mortality with either oestrogen + progestogen or oestrogen alone MHT.[6]

N.B. These data were published after the 2017 NAMS guidance.

Breast cancer

Key points about breast cancer risk and MHT:[1]

- The Women's Health Initiative trial found that oestrogen + progestogen MHT increased the risk of breast cancer (an absolute increase of < 1 case per 1,000 woman-years). Further analysis showed that this increased risk was only in women who had previously used MHT.
- Oestrogen-only MHT does not appear to increase breast cancer risk and some analyses have found possible reductions in risk
- The risks of breast cancer may be increased with longer durations, e.g. more than seven years, and higher doses of MHT.[7] The risk decreases after stopping MHT.[3]
- There is some evidence that the breast cancer risk may be higher with continuous progestogen use than with cyclical use[8]
- Micronised progesterone may be associated with a lower breast cancer risk than medroxyprogesterone
- The limited data available suggest that MHT does not further increase breast cancer risk in women at high risk, e.g. due to family history or BRCA mutations
- Prior COC does not appear to increase the risk of breast cancer in women using MHT[9]
- Other factors such as alcohol use and physical activity levels have also been shown to influence the risk of breast cancer, and ways to reduce risk can be discussed with women[4]

Undergoing screening for breast cancer with mammography is recommended every two years for females aged 45–69 years.[10]

N.B. The International Menopause Society (IMS) released a statement regarding a 2019 analysis on the association between MHT and increased breast cancer risk. The IMS noted that the analysis included primarily observational studies using older MHT regimens that do not reflect current recommendations and therefore have limited applicability to current practice. The statement is available here: **www.imsociety.org/manage/images/pdf/5054afeb9b1bc763032333443f1c0bed.pdf**

Cardiovascular disease

Coronary heart disease (CHD):* The effects of MHT on CHD vary depending on the woman's age or time since menopause when treatment was initiated.[1] For women aged < 60 years or fewer than 10 years since menopause, MHT may reduce the risk of CHD.[1] A Cochrane review found a 30% relative risk reduction in all-cause mortality and a nearly 50% relative risk reduction in CHD with MHT use when treatment was initiated within ten years of menopause.[11] Oestrogen alone appears to offer greater benefit than oestrogen + progestogen.[3] These treatment effects are no longer present when MHT is initiated more than ten years from menopause.[11] For women initiating MHT > 20 years since menopause, CHD risk may be increased, however, only in women taking combined oestrogen + progestogen MHT.[1]

* Composite of death from cardiovascular causes and non-fatal myocardial infarction

Stroke: The risk of stroke associated with MHT depends on the woman's age or time since menopause when treatment was initiated.[1] RCTs have shown no increased risk of stroke in women who start MHT aged < 60 years or within ten years of

menopause, but an increased risk if initiated after age 60 years or more than ten years from menopause.[1] The Women's Health Initiative trial found an absolute risk of stroke of < 1 per 1,000 woman-years in women aged < 60 years when they initiated MHT.[1]

Venous thromboembolism (VTE): Both oestrogen alone and oestrogen + progestogen MHT have been associated with a higher VTE risk across all ages, however, the absolute risk of VTE in women aged < 60 years is small (approximately 1 per 1,000 women per year, increased to 2 per 1,000 women per year when using oral MHT).[1, 12] Transdermal oestrogen, as well as lower doses of oral or transdermal oestrogen, are associated with lower VTE risk.[1] The absolute risk of VTE increases with increasing age; other factors such as smoking and obesity also increase VTE risk.[1]

Bone fracture

The use of MHT is associated with small reduction in fracture risk (all fractures combined), with 44 and 53 fewer fractures per 10,000 woman-years with oestrogen + progestogen and oestrogen alone, respectively, compared to placebo.[13] This reduced risk begins within the first few years of treatment.[14, 15] However, women at high risk of fracture should be prescribed bisphosphonates as a first-line treatment option, i.e. women with a previous fracture, a 10-year risk of hip fracture ≥ 3% or T-score of ≤ –2.5 from a dual energy X-ray absorptiometry (DEXA) scan.[16]

N.B. Participants in the Women's Health Initiative trials were not selected on the basis of having low bone density or osteoporosis. MHT lowered fracture risk in women with normal or low bone mineral density, not just in those with osteoporosis.

Information to help patients to consider the risks and benefits of MHT is available from:

- **www.menopause.org.au/health-info/menopause-videos**; videos from the Australasian Menopause Society
- **www.menopause.org.au/health-info/fact-sheets/what-is-menopausal-hormone-therapy-mht-and-is-it-safe**; PDF fact sheets and infographic print outs

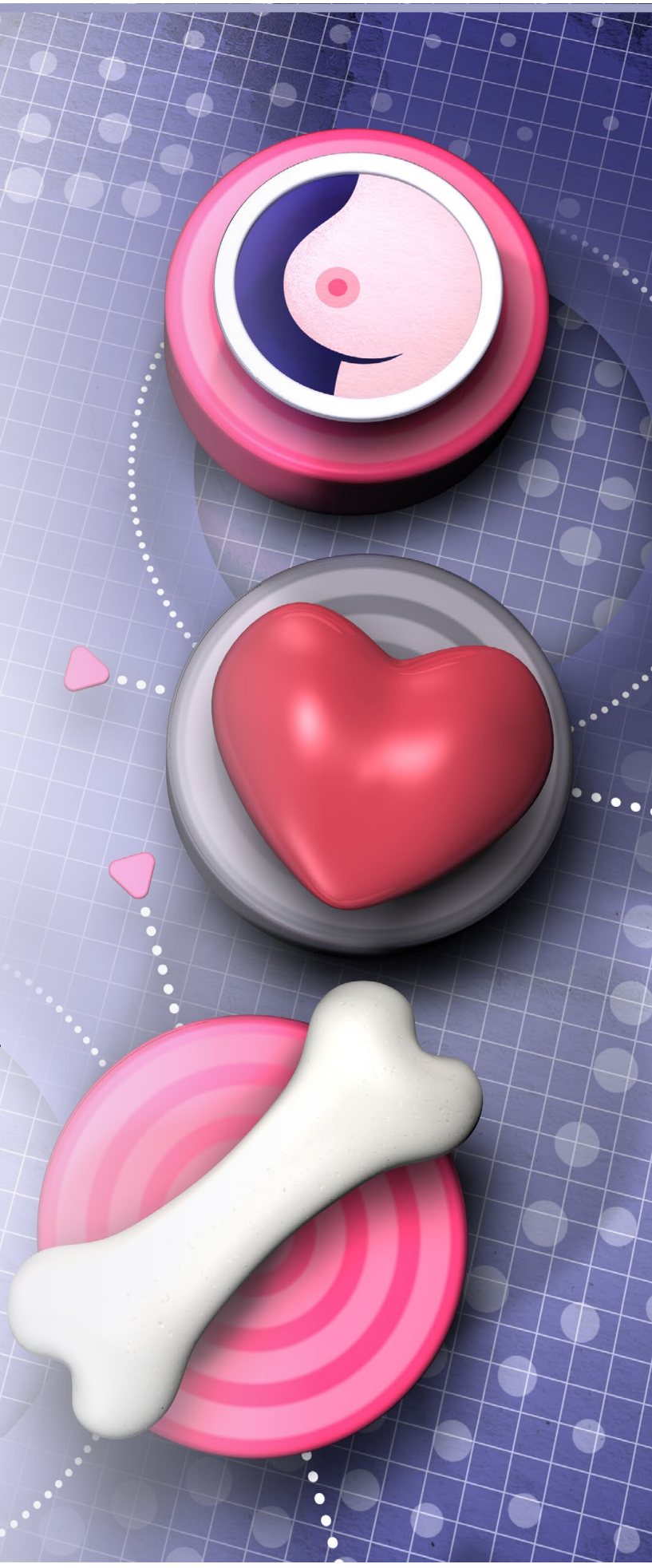

Table 1: MHT formulations available in New Zealand (as of October, 2024).[18]

	Route of delivery	Funding status*	Dose forms (refer to NZF for dosing regimens)
Oestrogen only products†			
Estradiol patch	Transdermal	●	25, 50, 75 or 100 micrograms/24 hours (applied twice weekly)
Estradiol gel	Transdermal	●	750 micrograms/actuation
Estradiol valerate tablets	Oral	●	1 mg, 2 mg
Estradiol tablets		◑	1 mg, 2 mg
Estriol		●	2 mg
Conjugated equine oestrogens		◑	300 micrograms, 625 micrograms
Progestogen only products			
Medroxyprogesterone acetate	Oral	●	2.5 mg, 5 mg, 10 mg
Norethisterone tablets (unapproved indication)	Oral	●	350 micrograms (Noriday), 5 mg (Primolut N)
Levonorgestrel IUD (Mirena)‡	Intrauterine	●	52 mg device
Progesterone capsule (micronised – Utrogestan)	Oral	●	100 mg
		○	200 mg
Combination products			
Estradiol + norethisterone tablets	Oral	◑	2 mg estradiol + 1 mg norethisterone
		◑	1 mg estradiol + 0.5 mg norethisterone
		◑	Cyclical (three doses): ■ 2 mg estradiol ■ 2 mg estradiol + 1 mg norethisterone ■ 1 mg estradiol

* Funding status: ● Fully funded, ◑ Partly funded, ○ Not funded

† Women with a uterus must also be prescribed a progestogen

‡ A 13.5 mg levonorgestrel IUD (Jaydess) is also available, however, this is not approved for providing endometrial protection as part of an MHT regimen

A range of fully funded, partly funded and non-funded MHT options are available

Table 1 shows the MHT options available in New Zealand. Refer to the NZF for dosing information: **www.nzf.org.nz/nzf_3855** and to Figure 1 for examples.

Choosing an oestrogen: Oestrogen should be initiated at the lowest dose. Transdermal estradiol is likely to be the most practical option due to the difficulty of dividing tablets to achieve a low dose, and the cost to the patient of other formulations that are not funded. Transdermal oestradiol also has a more favourable safety profile in terms of cardiovascular risk than oral oestradiol, particularly in older women.

Options for women beginning treatment with oestrogen include:

- 25 micrograms estradiol transdermal patch applied twice weekly, e.g. Monday and Thursday, (fully funded)
- 0.75 – 1.5 mg (1 – 2 actuations) estradiol transdermal gel, applied over a large area of skin, e.g. on top and bottom of arms from wrist to shoulder or inner thighs (avoid breasts or vagina), once daily
- 500 micrograms estradiol oral tablet, daily. This equates to half a tablet of the lowest strength available for many formulations and some tablets cannot be cut in half. Estradiol valerate (Progynova) 1 mg tablets are fully funded but efficacy is lost if they are divided. Estradiol 1 mg tablets (Estrofem) can be divided and are partly funded.
- 300 micrograms conjugated equine oestrogens oral tablet, daily, e.g. Premarin, partly funded

Choosing a progestogen: For women requiring combined oestrogen + progesterone MHT, this can be prescribed as:

- An oestrogen tablet, patch or gel with a separate formulation of oral progestogen – provides greater dose control than combination formulations (fully funded options available). The oral progestogen may be taken cyclically* or continuously (Figure 1).
- An oestrogen tablet, patch or gel with a levonorgestrel intrauterine system (Mirena – fully funded)† – provides progestogen without having to use an oral formulation; this option also provides contraception for women who may still become pregnant
- A combination oestrogen + progesterone formulation; cyclical and continuous formulations available (partly funded)

* A withdrawal bleed occurs towards the end of, or after, the progestogen treatment cycle. N.B Up to 25% of women will not have a withdrawal bleed.

† Suitable for five years' use when prescribed for endometrial protection as part of an MHT regimen[19]

A guide is available from the Australasian Menopause Society to assist with changing doses or formulations of MHT: **https://www.menopause.org.au/hp/information-sheets/ams-guide-to-equivalent-mht-hrt-doses-australia-nz**

Table 2: Suggested options for reducing adverse effects or improving the effectiveness of MHT.[17, 20]

Symptom or adverse effect	Suggested course of action
Persistent vasomotor symptoms	Increase MHT doses or trial another formulation
Breast tenderness	Reduce the dose of oestrogen or switch to another progestogen. If tenderness remains on further follow-up, consider discontinuing MHT or switching patients to tibolone (not funded).
Unscheduled bleeding within the first three months	Within the first three months of MHT: ■ Consider continuing treatment unless there is a high suspicion of endometrial cancer as bleeding may settle with time ■ Other options include: – Switching to cyclical progestogen for patients taking continuous progestogen – Increasing the dose of progestogen – Switching from oral progestogen to a levonorgestrel IUD After the first three to six months of MHT: ■ Organise further investigations for endometrial cancer ■ If no endometrial pathology is detected, consider increasing oestrogen dose

Transdermal oestrogen is associated with a lower risk of adverse effects

Transdermal application avoids first-pass metabolism and results in fewer effects on markers of cardiovascular risk than other formulations of oestrogen. Transdermal oestrogen should be considered first-line, particularly for women with:[17]

- Increased cardiovascular risk
- Increased risk of venous thromboembolism
- Hypertension
- Type 2 diabetes
- Obesity
- Hypertriglyceridaemia
- Migraine

Follow-up of patients prescribed MHT

Schedule a follow-up appointment after initiation of a MHT regimen, e.g. in one month, to assess treatment effect. Adverse effects of MHT include bloating, breast tenderness, increased blood pressure, headaches, fluid retention and urinary incontinence.[17] Changes in the dose or formulation of MHT may improve these symptoms (Table 2).

A guide is available from the Australasian Menopause Society to assist with changing doses or formulations of MHT: **https://www.menopause.org.au/hp/information-sheets/ams-guide-to-equivalent-mht-hrt-doses-australia-nz**

Unscheduled, heavy or irregular bleeding is common in the first three months of use of a continuous progestogen regimen, however, if it occurs after three to six months of use of any MHT regimen, consider endometrial cancer and perform or refer for pipelle biopsy and refer for ultrasound if appropriate.[20] If endometrial cancer is diagnosed, MHT must be stopped as this is a contraindication.[17]

If women develop urinary incontinence or have worsening symptoms while taking MHT but do not wish to discontinue treatment, pelvic floor muscle training may improve symptoms.[3] For women with primarily urogenital symptoms, switching to vaginal oestrogen treatments may improve urinary incontinence.[3]

Contraceptive needs for perimenopausal women

Contraception should be continued in sexually active women until one to two years after the last menstrual period or at age 55 years when a natural loss of fertility can be assumed (Table 3).[19]

The 52 mg levonorgestrel IUD (Mirena) can be used both as a contraceptive and to provide endometrial protection as part of a MHT regimen. When prescribed for endometrial protection, the IUD should be replaced after five years. If used solely for contraception, a 52mg levonorgestrel IUD can be left in place until the age of 55 years if it was inserted at age 45 years or over.[19] Extended use of the smaller 13.5mg levonorgestrel IUD (Jaydess) is not recommended due to a lack of data on effectiveness as a contraceptive beyond the approved duration of use.[19]

Table 3: Guidance on the choice of contraceptive for females approaching menopause. Adapted from the Faculty of Sexual and Reproductive Healthcare.[19]

Contraceptive method	Recommendation for discontinuing due to natural loss of fertility
Non-hormonal methods: ■ Condoms ■ Copper intrauterine device (IUD)*	Can be stopped after amenorrhoea of: ■ One year for females aged ≥ 50 years ■ Two years for females aged < 50 years
Progestogen-only methods: ■ Pills ■ Implant ■ Levonorgestrel IUD	Can be used until age 55 years or stopped between age 50–55 years on the basis of FSH test results**
The combined oral contraceptive pill and medroxyprogesterone acetate injections are not recommended from age 50 years onwards, as alternatives are available with fewer risks.	

* A copper IUD inserted after the age of 40 years can be used until contraception is no longer required

** FSH: follicular stimulating hormone. For patients with FSH levels of ≥ 30 IU/L, progestogen-only methods should be used for one more year and then can be discontinued

Other treatment options for menopause symptoms

Other pharmacological treatment options may be considered for women with contraindications to MHT or those who do not wish to use it. Lifestyle changes to manage menopause symptoms should be discussed with all women.

Lifestyle changes

Lifestyle changes, e.g. avoiding triggering foods or drinks, smoking cessation, weight loss and exercise, are a low risk approach that may help menopausal symptoms and reduce risks of chronic disease. Psychological techniques such as cognitive behavioural therapy, mindfulness and hypnosis have been shown to improve vasomotor symptoms of menopause.[22]

Vaginal treatments are effective for urogenital symptoms

For women who principally have urogenital symptoms, non-hormonal vaginal moisturisers (e.g. Replens) and lubricants can assist with vaginal dryness, itching or pain during intercourse. These are available over-the-counter (not funded). If non-hormonal options do not provide adequate symptom relief, a 0.1% estriol cream or 500 microgram estriol pessary are available fully funded.[18] These have fewer risks than systemic hormone treatment and can be prescribed without the addition of a progestogen in females with a uterus.[17, 21]

Vaginal oestrogen formulations may be prescribed with caution to patients with a history of hormone-dependent cancer, e.g. breast or endometrial cancer, as they do not increase serum oestrogen levels beyond the normal menopausal range. However, they should only be used if patients have trialled other non-hormonal approaches and consultation with the patient's oncologist may be appropriate.[23]

Other pharmaceutical options

Various other pharmacological treatments options are available to help manage the vasomotor symptoms of menopause, with varying levels of evidence supporting their effectiveness. This includes:[24]

- Selective serotonin or serotonin-noradrenaline reuptake inhibitors, e.g. paroxetine,* citalopram, escitalopram and venlafaxine
- Tibolone (not funded)
- Clonidine
- Gabapentin or pregabalin†
- Oxybutynin†

* Avoid in women using tamoxifen as it may affect the conversion of tamoxifen to its active metabolites[25]

† Unapproved indication

Complementary and alternative medicines

A range of over-the-counter supplements, remedies or alternative medicines are marketed for the treatment of menopausal symptoms, e.g. St. John's Wort, maca, phytoestrogens. However, none of these are as effective as oestrogen treatment for menopausal symptoms.[26] If women enquire about non-pharmacological options, consider whether there is any evidence of effectiveness, safety, contraindications and potential for medicines interactions.

"Bioidentical" hormones are not recommended

"Bioidentical" hormones are synthesised to have the same chemical composition as hormones produced by the body. These are prepared by a compounding pharmacist as creams or troches (dissolvable lozenge), and are often marketed as "natural" and "safer" alternatives to "synthetic" hormones.[27] However, these products are unregulated; there is no requirement for the same testing and safety data as for conventional MHT medicines, and there is no consistency of dosing.[4] There is also little evidence to show that these are effective. For example, transdermal wild yam creams are promoted as a natural source of progesterone. They contain diosgenin, a steroid with no hormonal activity, which can be synthesised into progesterone in a laboratory setting. However, the human body is unable to do this and the cream can therefore have no beneficial effect on menopause symptoms.

Continued use of MHT should be reviewed at least annually. Discuss menopausal symptoms and reassess whether continuing use is appropriate, or dose adjustments need to be made. Update any new family history, e.g. breast cancer, as this can influence the benefit-risk ratio.[4] Ensure women are having regular mammograms; screening for breast cancer with mammography is recommended every two years for females aged 45–69 years.[10]

Discontinuing MHT

Gradually taper the dose when MHT is withdrawn, e.g. by changing to a lower dose formulation or to alternate day dosing, as this can reduce the short term incidence of menopausal symptoms and may be better tolerated by patients.[21] Remind women of sleep hygiene approaches to minimise any sleep disturbances associated with MHT withdrawal.

Women who require fracture prevention should switch to another treatment, e.g. a bisphosphonate, as the protective effect of MHT on bone mineral density declines after treatment is stopped.[3]

Acknowledgement: Thank you to **Dr Anna Fenton**, Gynaecological Endocrinologist, Canterbury DHB for expert review of this article.

N.B. Expert reviewers are not responsible for the final content of the article.

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