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Menopause Treatment Options

This document contains information on pre-menopause, peri-menopause and menopause, as well as lifestyle factors that can be of benefit and available hormonal and non-hormonal treatment options.

In recent years, one of the most important shifts in menopause research and treatment is the recognition that body-identical hormone treatments have proven to be much safer than synthetic hormone treatments. This is something that the doctors at the Centre have supported since our inception in 2003. This has also meant that commercially produced TGA-registered body-identical hormones are available in specific doses.

Best practice menopause treatment should be patient centred and specific for her needs. As such, treatment options, dosing and length of treatment should be considered based on the individual's symptoms, circumstances, and expectations.

Below is some information about the different stages of menopause, practical strategies as well as information about treatment options.

The Stages of The Menopause

Hormones are chemicals made in your body, which send out messages through the bloodstream. The hormones of relevance at menopause are oestrogen and progesterone. The symptoms of menopause are due to changes in the levels of these hormones, which usually happens over months or years as you approach menopause. If menopause is induced by surgery or cancer treatment, there can be a sudden drop in all these hormones, causing symptoms to be more severe.

1. Perimenopause

This is the lead-up to the menopause (running out of eggs). A woman may start experiencing changes in her menstrual periods such as irregular periods or changes in flow. Cycles can be shorter or longer in length. Symptoms may also include hot flushes and night sweats, aches and pains, fatigue, or irritability as well as premenstrual symptoms such as sore breasts. These changes may be caused by fluctuations in the production of hormones from the ovary. Some women can experience menopausal symptoms for 5-10 years before their final menstrual period[1]. There is no way to predict the age at which a woman's menopausal symptoms will start or how long they will last.

2. The menopause

This relates to the final menstrual period (no more eggs).

3. Post-menopause

This starts when you have had no periods for 12 months or more.

No two women will experience the menopause in the same way. Culture, health, previous experience of mood problems, lifestyle and whether you have had a natural, surgical, or chemotherapy-induced menopause will all affect the experience of menopausal symptoms.

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What Can You Do to Help with The Menopause?

- Be aware of practical strategies to stay cooler, such as carrying a hand fan or water facial spray and wearing layers of clothing to peel off when you are hot
- A healthy lifestyle can help to reduce symptoms of menopause:
    - a nutritious diet helps with fatigue and moodiness
    - being physically active helps with stress and mood
    - keep an eye on your alcohol and caffeine intake, as they are known to make hot flushes worse
    - weight loss can help reduce hot flushes
- Keep a record of the physical and emotional symptoms troubling you and list their frequency and effect on your daily life. This information can help clarify what changes you can make to reduce their impact
- Talk to your doctor about menopausal hormone therapy. Risks and benefits should be considered when deciding with your doctor whether to use menopause hormone therapy (MHT)
- If you cannot take MHT, other medications such as antidepressants – selective serotonin (SSRIs) or norepinephrine reuptake inhibitors (SNRIs) – and a chronic pain medicine can reduce hot flushes
- Seek advice on complementary therapies that may help, including:
    - herbal and natural remedies: the herb black cohosh and eating phytoestrogens (eg, soy, lentils) may help with hot flushes; St John's Wort may help with mood changes at the menopause. The safety and effectiveness of other herbal remedies are not proven
    - cognitive behaviour therapy has been found to be effective in reducing the intensity and frequency of hot flushes, sweats and insomnia, with improvement in quality of life
    - hypnotherapy has also been shown to reduce hot flushes and sweats
    - relaxation: practising relaxation and controlled breathing may help hot flushes
- Look after your emotional health along with your physical health
- Depending on your symptoms, you may like to see a general practitioner, a gynaecologist, endocrinologist (hormone specialist), registered naturopath, psychologist or dietitian.

The Risks and Benefits of Menopause Hormone Therapy (MHT): A Historical Perspective

- The first major study of MHT was the Nurses' Health Study, conducted in women aged 30 to 55 years at entry[1]. The advantages of this study were that MHT was used from the time of menopause. The disadvantage was that it was an observational study. However, the findings of this study, i.e. that MHT is associated with reduced mortality, particularly that from cardiovascular disease, prompted the subsequent randomised controlled trials.

- The Women's Health Initiative (WHI) evaluated the impact of menopausal hormone therapy on cancer, cardiovascular disease, and osteoporotic fractures was conducted in women aged 50 to 79 years at entry. The study was terminated early (July 2002), as the researchers felt the risks outweighed the benefits. The study reports indicated that menopausal hormone therapy (specifically combination of non-bioidentical oral oestrogen and non-bioidentical progestin) increased the risk of Deep Vein Thrombosis (DVT), stroke, breast cancer and myocardial infarction[2,3]. In particular, the finding of increased cardiovascular morbidity in the WHI tipped the perceived balance of risk and benefit toward risk.
- As a result of the findings of the WHI many doctors and their patients abandoned the use of menopausal hormone therapy.
- Manson, in the 2013 follow up overview of the findings from the WHI, concluded as follows: "Menopausal hormone therapy has a complex pattern of risks and benefits. Findings from the intervention and extended post-intervention follow-up of the two WHI hormone therapy trials do not support use of this therapy for chronic disease prevention, although it is appropriate for symptom management in some women"[4].
- A recent Cochrane review of the studies of MHT and its relationship to cardiovascular risk has concluded that there was no strong evidence for protection or harm from MHT with respect to cardiovascular disease[5]. However, in women who start MHT less than 10 years post menopause, there was some evidence of protection for mortality (RR 0.70, 95% CI 0.52 to 0.95) and coronary heart disease (RR 0.52, 95% CI 0.29 to 0.96), providing support for the so-called "timing hypothesis".

Summary of WHI Findings

- Transdermal MHT has not been associated with an increase in risk of venous thromboembolic disease whereas oral MHT has[6,7]
- Starting MHT in the first 10 years after menopause carries no increase in cardiovascular risk and may confer some cardiovascular protection
- The addition of progestogen reduces the risk of endometrial cancer but increases the risk of breast cancer
- Different progestogens have different risk ratios for breast cancer increase and some, e.g. micronized progesterone and dydrogesterone, are safer than others[8].

Non-Hormonal Treatment Options

Many women request non-hormonal treatments for menopausal symptoms. These treatments are largely prescribed "off-label". Off-label means use outside the specific purpose for which the drug was approved by Australia's medicines regulator, the Therapeutic Goods Administration.

Most non-hormonal treatments only treat hot flushes and night sweats. There are also non-hormonal treatments for vaginal dryness.

Antidepressants

Several types of antidepressants (SNRI and SSRIs explained below) have been noted in small, short-term studies to reduce hot flushes. Four weeks is sufficient to establish whether these products will

be effective in reducing hot flushes. These medications should not be taken with any other antidepressants or any substance containing St. John's Wort and discontinuation should be tapered.

- Venlafaxine and Desvenlafaxine are serotonin-noradrenaline reuptake inhibitors (SNRIs). Serotonin and noradrenaline, known to affect mood, may also impact thermoregulation
- *Side-effects* include dry mouth, nausea, sleep disturbances, loss of appetite and constipation. Venlafaxine should not be used in women with heart disease, electrolyte imbalance or uncontrolled high blood pressure. Blood pressure should be monitored while taking it and discontinuation should be tapered.

Gabapentin

Gabapentin is an anticonvulsant (an analogue of gamma-aminobutyric acid). It is approved to treat neurological disorders such as seizures and neuropathic pain.

- *Research:* A systematic review has confirmed that Gabapentin 900mg per day reduces hot flushes more effectively than placebo[19]. The most common side effect of gabapentin is somnolence, and women may prefer to take it at night.
- *Side-effects* include rash, dizziness and excessive sleepiness which tends to improve over time. The drug can also cause swelling of the lower limbs and weight gain. Discontinuation should be gradual over a week.

Clonidine

Clonidine is a centrally acting alpha adrenergic agonist which stimulates particular brain receptors and has been used for many years to lower blood pressure and prevent migraine as well as treat hot flushes.

- *Research:* Several randomized controlled trials have shown that clonidine is more effective than placebo for hot flushes, but side effects may limit tolerability. Both tablets and transdermal (skin patches) have been tested. Several small studies showed reduced hot flushes at eight weeks (38% for clonidine versus 24% for placebo). Patches reduced flushes by 80% compared to 46% for oral clonidine, however the patches are not available in Australia. Two larger studies of breast cancer survivors taking tamoxifen showed reduced frequency of flushes with oral and transdermal clonidine compared to placebo.
- One recent study comparing clonidine to venlafaxine in breast cancer patients has shown equal efficacy but better tolerability for clonidine[20].
- *Side-effects* include dry mouth, drowsiness, dizziness, constipation and difficulty in sleeping. Advice is to stop clonidine if there is no benefit after four weeks. High doses should be tapered gradually to avoid side-effects like raised blood pressure.

Menopausal Hormone Therapy

In a woman with an intact uterus, unopposed oestrogen therapy increases the risk of endometrial hyperplasia and cancer[9]. Therefore, women who have not had a hysterectomy should take a progesterone as well to provide endometrial protection.

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Types of Oestrogens

- Oestrogens are available as tablets, skin patches, and gels.
- Patches or gels may be better for those with gut absorption problems.
- Patches or gels are also better for those who have high triglyceride concentrations or who are at risk of deep vein thrombosis (DVT). This includes those who are overweight and smokers.
- Vaginal oestrogen in creams, pessaries or tablets is available for vaginal dryness or dyspareunia.
- Examples of non-body identical oestrogens include
    - Progynova
    - Premarin

Types of Progestogens

- The term "progestogen" encompasses both bioidentical progesterone and synthetic preparations which act on the progesterone receptor. The term "progestin" is used purely for the synthetic preparations.
- Progestogens are mostly taken orally. The only progestogen which is reliably absorbed through the skin is norethisterone, used in the combined MHT patches. Progesterone creams are not reliably absorbed and do not confer adequate endometrial protection.
- Micronised progesterone capsules (Prometrium) are a form of bioidentical progesterone recently available in both Australia and New Zealand.
- Examples of non-body identical progestogens include:
    - Provera
    - Primolut N
    - Ralovera

Types of Oestrogen-Progestin Combinations

- Femoston
- Trisequence
- Angeliq
- Kliovance
- Kliogest

Other Menopausal Hormone Therapies

- Tibolone is a synthetic progestogenic hormone which, once metabolized, acts like oestrogen, progestogen and testosterone.
- Testosterone – is sometimes added to MHT and may improve libido and energy in some women.

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The Benefits of Menopausal Hormone Therapies (MHT)

- MHT is the most effective treatment for hot flushes and night sweats.
- MHT also effectively treats vaginal dryness.
- Reducing menopausal symptoms with MHT may improve quality of life.
- MHT reduces the risk of postmenopausal bone fracture, including hip fracture[4].
- MHT use is not associated with weight gain[11].

Managing the Risk

- Regular breast checks and screening mammograms should be performed in women over 50 years whether they are taking MHT or not.
- MHT should be reviewed annually.
- If a woman using MHT develops symptoms suggesting DVT or stroke, she should stop the MHT and seek medical attention.
- Oral MHT increases the risk of DVT. In women less than 60 years the risk is low. The risk increases with age and other risk factors such as obesity, previous thromboembolism, smoking and immobility. The risk is less with the use of transdermal preparations and with the use of oestrogen alone[10].
- The risk of breast cancer is primarily associated with combined oestrogen/progestogen therapy and related to the duration of use. The risk of breast cancer attributable to combined MHT is small and decreases after treatment is stopped. Oestrogen alone has not been shown to increase breast cancer risk in high quality randomized controlled trials.
- Oral MHT increases the risk of stroke and the risk increases with age. Stroke risk is not significantly altered in women younger than 60 years with normal blood pressure. The risk may be less with the use of oestrogen gel or skin patches.
- Cessation of MHT is associated with increased cardiovascular and cerebrovascular events and increased risk of fracture[12,13].

Oestrogen Formulations

Oestrogens are available as tablets, skin patches and gels. These products contain different kinds of oestrogen (oestradiol, conjugated equine oestrogen or oestriol).

Patches or gels are better for those who have high triglyceride concentrations, those with hypertension, those who may not absorb tablets adequately and those at increased risk of DVT. This includes those women who are overweight or smokers[6].

Vaginal oestrogen in creams, pessaries or tablets is available for women with symptomatic vaginal dryness and can be used either alone or in combination with systemic therapy[14].

The Benefits of Oestrogen

- Oestrogen reduces the severity and frequency of hot flushes by around 85%.
- Oestrogen improves vaginal dryness.
- By reducing menopausal symptoms, oestrogen may improve sleep and quality of life.

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- Oestrogen reduces the risk of post-menopausal bone fracture, including hip fracture[4].
- Oestrogen use is not associated with weight gain[11].

Side-Effects of Oestrogen

Common side-effects, which are usually temporary, include breast enlargement and tenderness, and nausea. This may be dose related. Oral oestrogen may be associated with exacerbation of hormonally sensitive migraine headache.

The Risks of Oestrogen

Oral oestrogen increases the risk of blood clots DVT. The risk increases with age and other risk factors such as obesity, previous thromboembolism, smoking and immobility. In women less than 60 years, the risk with oral oestrogen alone is 3 per 10,000 per year which is not significantly different from placebo.

- Oral oestrogen increases the risk of stroke and the risk increases with age. Stroke risk is not significantly increased in women younger than 60 years with normal blood pressure. The risk may be lower with lower doses and the use of transdermal oestrogen[15.]
- Oral oestrogen is associated with an increased risk of gallbladder inflammation (cholecystitis). There are no data regarding gel or skin patches.
- Oestrogen alone does not appear to increase the risk of breast cancer. The risk of breast cancer is primarily associated with combined oestrogen/progestogen therapy and related to the duration of use. Oestrogen alone has not been shown to increase breast cancer risk in high quality randomized controlled trials[16].In a large observational study, there was no significant increase in breast cancer with oestrogen only therapy for 20 years[17].
- Oestrogen alone commenced at the time of menopause does not increase the risk of coronary heart disease and may decrease the risk[18].

Selective Oestrogen Receptor Modulators (SERMs)

SERMs is “shorthand” for a class of drug called selective oestrogen receptor modulators. They are a versatile group of drugs that can be used to treat/ prevent a number of conditions such as osteoporosis, infertility and hormone responsive cancers. Within the SERM class, different compounds have differing agonist or antagonist effects at the oestrogen receptor in different tissues, therefore they are “selective”[21,22].

Different Kinds of SERMs

- Naturally occurring SERMs include plant-derived oestrogens or phyto-oestrogens that are sometimes used to treat symptoms of menopause.
- Newer SERMs are being developed with more favourable oestrogen receptor selectivity i.e. utilizing the positive effects of oestrogen such as preventing osteoporosis and treating genital atrophy (vaginal dryness), without stimulating breast cancer cells or inducing endometrial hyperplasia. Raloxifene is already available in both Australia and New Zealand.

Raloxifene

- Raloxifene has been shown in clinical trials to increase bone density in the spine and hip and to reduce the risk of spinal fractures in women with osteoporosis[23].
- Unlike tamoxifen, raloxifene is anti-oestrogenic in the uterus so it does not have an increased risk of endometrial cancer. It is unlikely to cause bleeding or spotting.
- Raloxifene has been shown to reduce the risk of invasive breast cancer by 70% in women who are taking it for osteoporosis or who are at increased risk of developing breast cancer, with fewer side effects than tamoxifen.
- Raloxifene lowers serum total and LDL cholesterol but does not affect HDL cholesterol or triglyceride levels

Risks and side-effects of raloxifene

- Raloxifene does not improve menopausal symptoms and, may in fact worsen them. Its use is therefore limited to postmenopausal women who do not have troublesome symptoms of menopause. Side-effects include hot flushes, leg cramps and swelling of the legs.
- Raloxifene does not reduce the risk of peripheral fractures.
- Like oral oestrogen, raloxifene slightly increases the risk of DVT, and has been shown to increase the risk of fatal stroke in women with coronary artery disease (CAD) or at high risk of CAD.

Ospemifene

- Ospemifene is an oestrogen agonist in the vaginal epithelium and is used to treat vaginal dryness. It is taken as a tablet once daily. The most common side effects include flushes, sweats and, muscle cramps[24].

Body Identical Commercially Available Hormone Therapy

'Body identical' hormone therapy refers to a hormone that is identical to those produced by the body. These are TGA approved treatments and have a documented profile of benefit as well as short term and long-term risk. Commercially available body-identical oestrogen is available in Australia as tablets, transdermal patches or gel in specific doses. Examples of these include Estraderm, Estradot, Climara, Estrogel and Sandrena gel. It is also available for topical vaginal treatment – Ovestin and Vagifem. Commercially available body-identical progesterone is now available in capsule form in Australia (as Prometrium). Prometrium is currently available as a 100mg capsule. Many of the studies/research available on commercial products do not extend to bioidentical hormones alone, as they predominately focus on synthetic hormone preparations. In studies that use bioidentical hormones, it does appear that the health outcome is more favourable compared to the synthetic alternative.

Bioidentical Compounded Hormone Therapy

These products are compounded to an individual prescription from your doctor. Although the active constituents are pharmaceutical USP grade bioidentical hormones, the preparations are not individually TGA approved. Some large cohort studies have been conducted on patients using compounded bioidentical hormones and these studies have contributed to the development and

controlled trials of set dose products that have been listed on the TGA register. However, because each prescription is compounded for an individual's needs, there is no data available from controlled studies on these specific preparations regarding efficacy and safety.

Compounded bioidentical hormones may provide an option for patients where a commercial/pharmaceutical product does not achieve the desired therapeutic outcomes for patients and an alternate strength or mode of application, which is not commercially available, is indicated.

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