CLINICAL PRACTICE GUIDELINE

Menopause & menopausal symptoms

This document should be read in conjunction with this Disclaimer

Contents

Menopause
Assessment of the woman algorithm

Purpose: To identify which assessments are required when a woman presents at the menopause clinic.

Assessment required at the presentation of the midlife woman

Medical History

Relevant Gynaecological Facts
- Bleeding pattern or LMP
- Past surgery (hysterectomy / oophorectomy)
- Current use of hormonal therapy including contraception

Personal Medical Issues
- DVT / PE
- Cancer (Breast / Gynaecological)
- Cardio / cerebrovascular disease
- Hypertension
- Liver disease
- Osteoporosis / fractures
- Diabetes
- Thyroid disease
- Depression / anxiety / PND
- Recurrent UTI's

Family History
- DVT / PE
- Cancer
- Cardio / cerebrovascular disease
- Osteoporosis

Other
- Social history
- Current medications (+OTC)
- Smoking
- Alcohol
- Diet
- Exercise
- Allergies

Examination
- Height and weight
- Blood pressure
- Breast examination
- Pelvic examination if clinically indicated

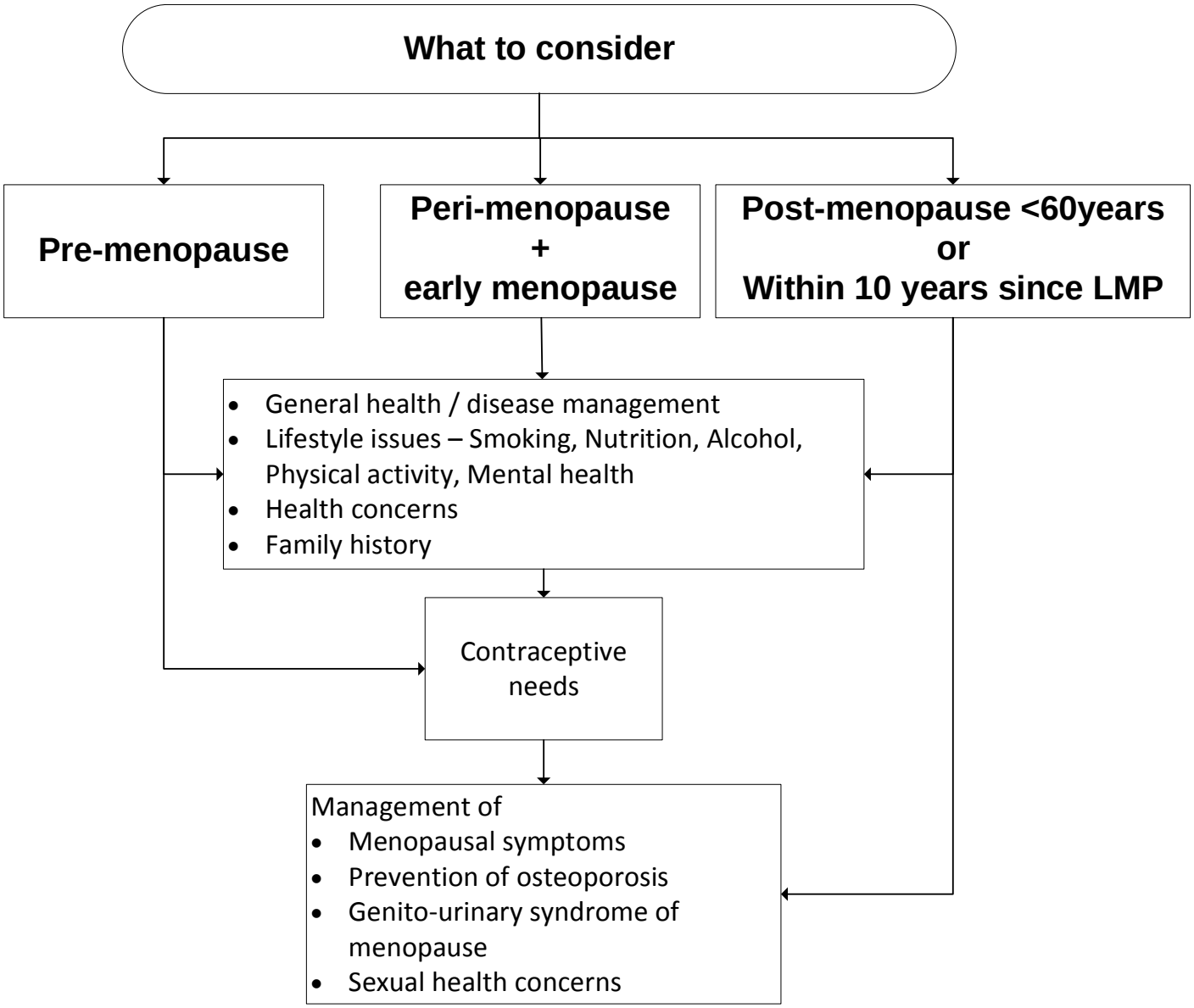
Investigations required for Menopause Clinic appointment
- FBP and Iron studies
- Lipid profile
- Fasting glucose
- TSH
- U&E, LFT
- Vit D in at-risk women
- Recent MMG (in last 2 years)
- Completed recent cervical screening (Pap or CST)

Note: Female hormone profile not routinely required but is essential if Premature Ovarian Insufficiency (POI) is suspected in women <40 years

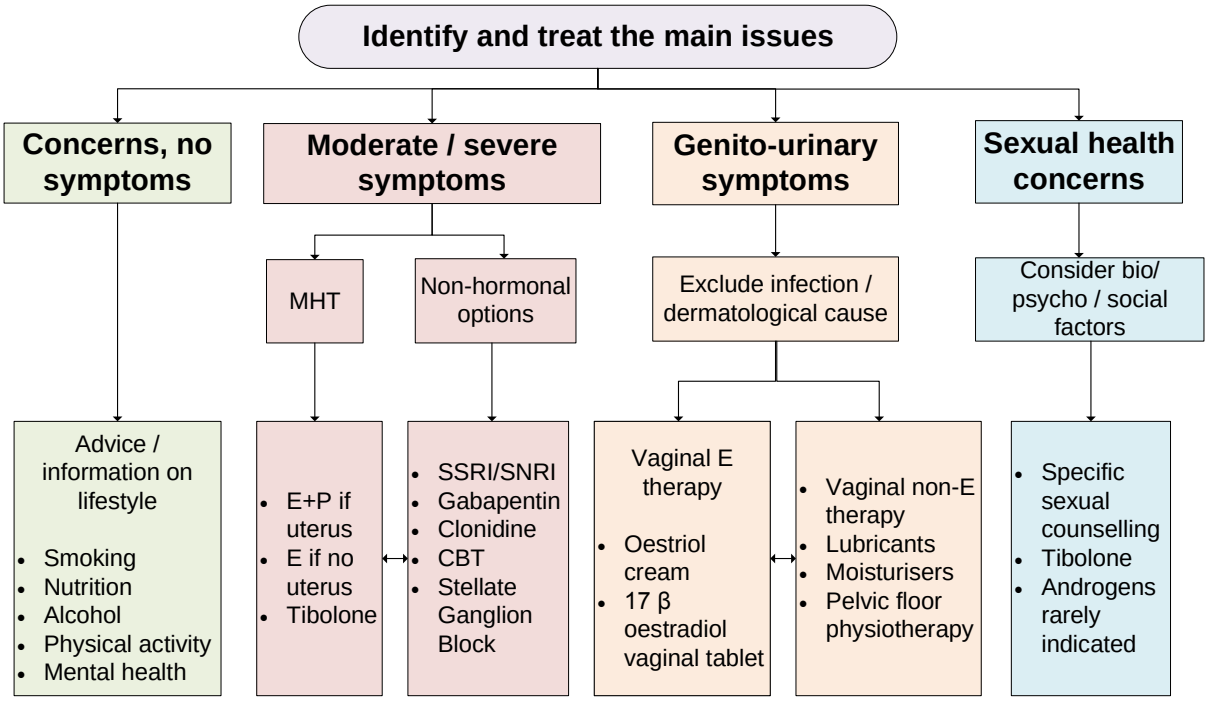
Abbreviations:

CST:	Cervical screening test
DVT:	Deep venous thrombosis
FBP:	Full blood picture
LFT:	Liver function tests
LMP:	Last menstrual period
MMG:	Mammogram
OTC:	Over the counter
PE:	Pulmonary embolus
PND:	Postnatal depression
TSH:	Thyroid stimulating hormone
U&E:	Urea & electrolytes
UTI:	Urinary tract infection

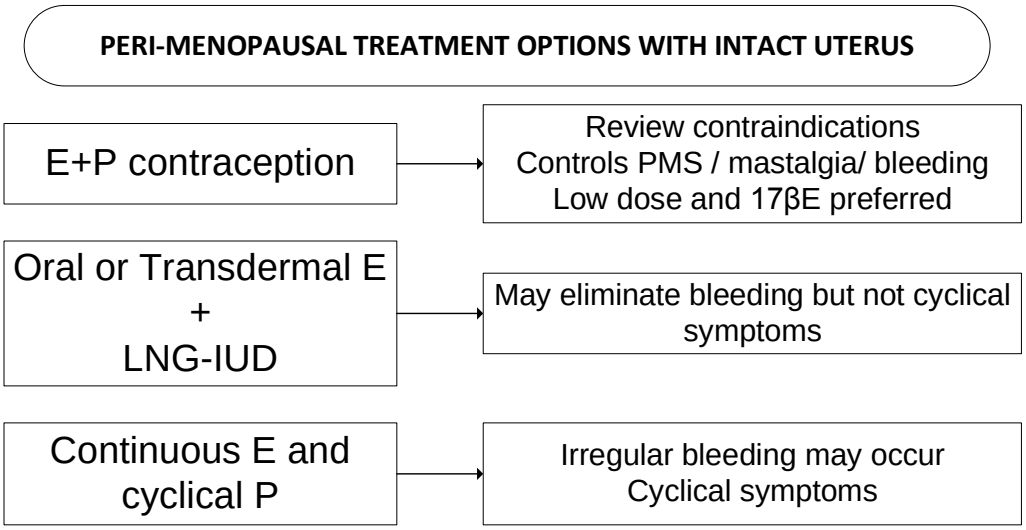
Considerations



Menopause symptom management



Peri-menopausal treatment



Abbreviations:

CBT:	Cognitive behavioural therapy
E:	Estrogen
LNG-IUD:	Levonorgestrol intrauterine device
MHT:	Menopause hormonal therapy
P:	Progesterone
PMS:	Pre-menstrual syndrome
SSRI:	Selective serotonin reuptake inhibitor
SNRI:	Serotonin–noradrenaline reuptake inhibitor

Menopausal hormonal treatment

Menopause hormonal treatment (MHT)

Uterus intact

A. Combined transdermal patch (E+P)

B. Transdermal (E) patch or gel + Oral P or LNG-IUD

C. Oral E + Oral P or LNG-IUD

D. Tibolone (after 12 months of amenorrhoea)

Micronised oral Progesterone is now available in Australia

Post-hysterectomy

A. Transdermal E patch or gel

B. Oral E

C. Tibolone

Add Progesterone for women with a history of endometriosis

Caution with initiating MHT

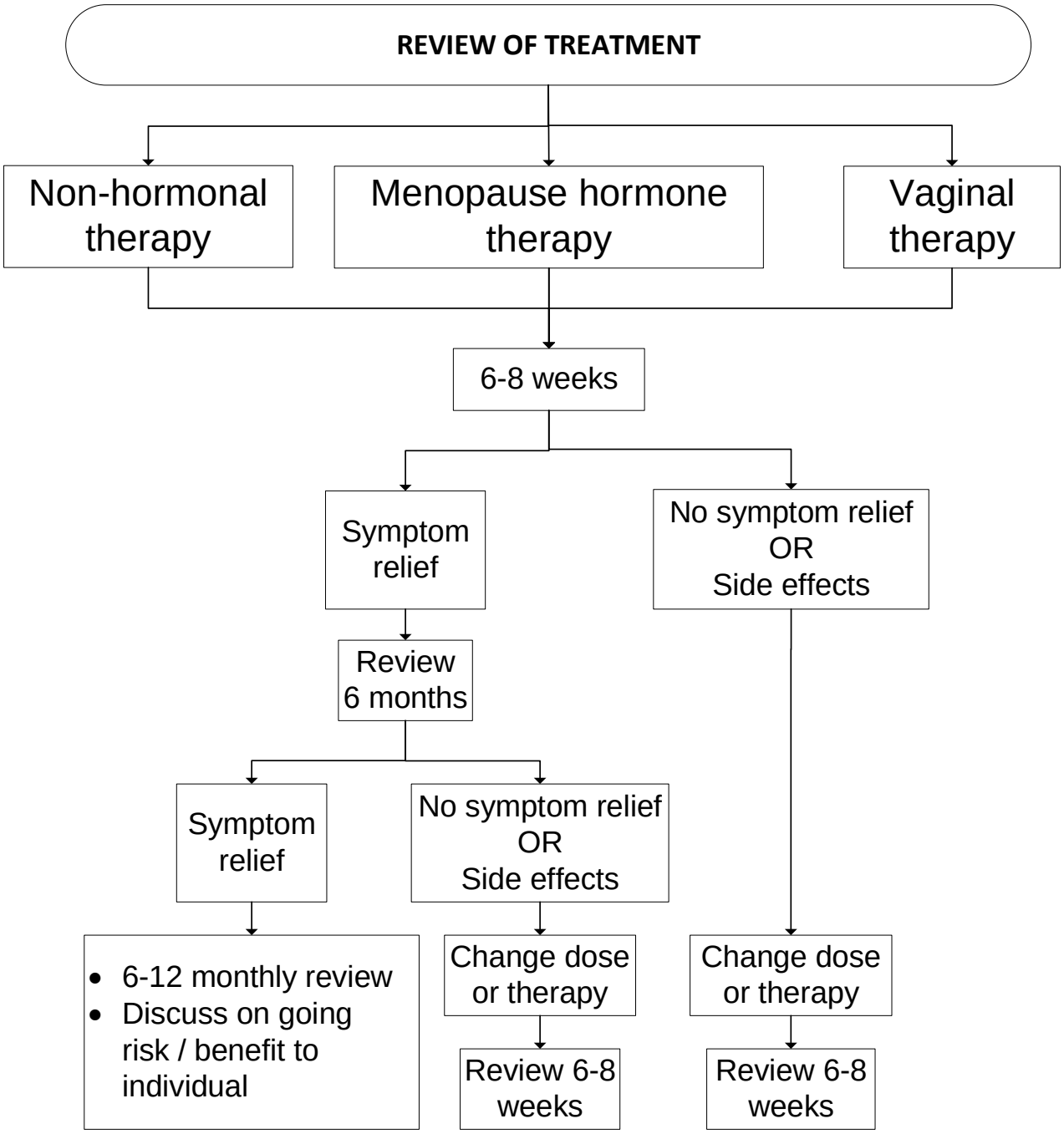
- Women > 60 years of age
- > 10 years since LMP

Contraindications to MHT

- Oestrogen-dependent cancer
- High risk of DVT / VTE or known thrombophilia
- Undiagnosed vaginal bleeding
- Active liver disease
- Untreated hypertension
- Personal wish not to use hormones

Abbreviation:
VTE: Venous thrombo embolism

Menopause: Review of treatment[1]



Acknowledgment- Women's Health Research Program. 2014. School of Public Health and Preventative Medicine. A Practitioner's Toolkit for Managing the Menopause

Menopausal symptoms after cancer

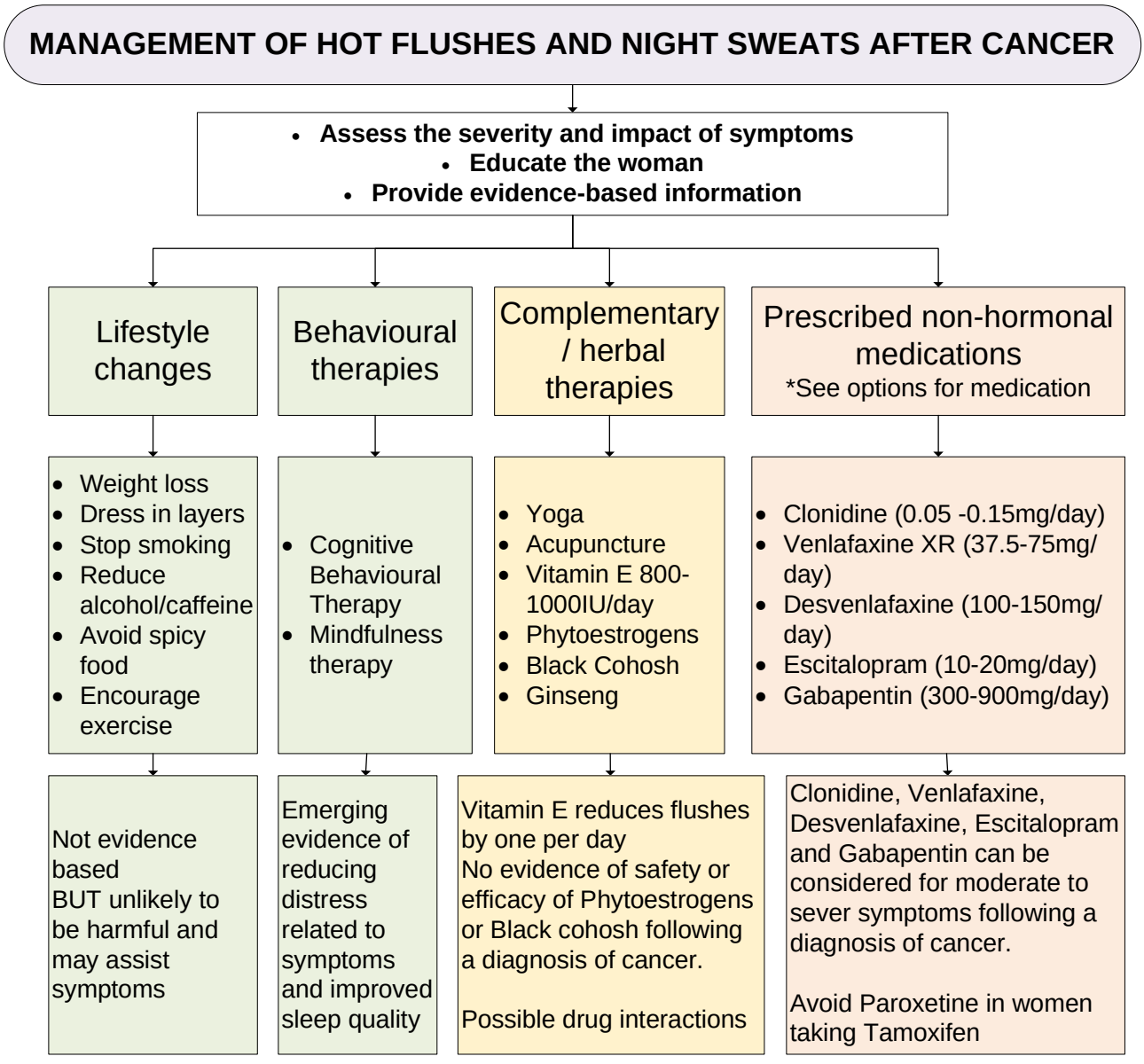
Breast or gynaecological cancer

Aim

- To guide menopausal symptom management after cancer, including hot flushes, vaginal dryness, sexual dysfunction and bone loss.

Hot flushes

The pathophysiology of hot flushes is poorly understood but may be linked to the instability of the hypothalamic thermoregulatory centre induced by estrogen withdrawal. Low circulating levels of estrogen are not directly related to hot flushes but estrogen may control thermoregulation via serotonin receptors.



Vaginal dryness

1. Vaginal lubricants

Vaginal lubricants are designed for use during sexual intercourse. Examples of these include Astroglide or silicone-based lubricants such as Pjur©.

2. Vaginal moisturisers

Vaginal moisturisers are developed to provide relief from the symptoms of vaginal atrophy such as dryness, itching and irritation and dyspareunia.

Replens© is a long-lasting, hormone free vaginal moisturiser that is applied internally three times a week. Replens® is available at community pharmacies without a prescription. At KEMH Pharmacy, 3 months' supply of Replens® may be supplied at a time if the prescriber has endorsed the prescription with "Regulation 24". It is available at pharmacies, without prescription, in packs of 10.

Women who do not achieve relief with Replens may consider hormone-free, paraben-free hyaluronic acid gel (Hyalofemme®). Hyalofemme® is a Special Access Scheme (SAS) Category B medication, that requires a prescription and an SAS Category B form to be completed before supply can be obtained.

A compounded hyaluronic acid product is also available under special circumstances. The compounded product takes approximately a week to order and has an expiry of only one month. A prescription and an Individual Patient Application (IPA) form must be completed before supply of the compounded product can be obtained.

3. Vaginal estrogen

Evidence suggests that topical estrogen effectively alleviates vaginal dryness and reduces dyspareunia. As topical estrogen does not appear to stimulate the endometrium, additional progestogens are not required.

Although short term use of topical estrogen has not been shown to be associated with increased risk of breast cancer recurrence, recent data suggests that for women on aromatase inhibitors serum estradiol rises. This effect reverses the estrogen suppression achieved by aromatase inhibitors and may partially negate the benefit of aromatase inhibitors [2].

For more information regarding products, dosing and administration, refer to KEMH Adult Medication Monograph: Vaginal Estrogen (Oestrogen)

Recommendations for practice

Topical estrogens in the form of estriol (e.g. Ovestin) may be used following treatment for breast cancer in women who are prescribed Tamoxifen.

Women using aromatase inhibitors should be advised that vaginal estrogen may impact on the efficacy of their endocrine therapy[2].

Topical estrogen is not necessarily contraindicated following a gynaecological malignancy. Discuss with treating Gynaecologic Oncologist / Oncologist.

Sexual dysfunction

Sexual dysfunction is commonly associated with menopause and cancer.

After menopause, vaginal dryness, lack of arousal, dyspareunia and difficulty with orgasm are common. Women who have had treatment for cancer may have issues with body image, health concerns and fatigue. These factors and others can affect libido and sexual satisfaction.

As part of the routine assessment obtain:

- Sexual history and any relevant issues
- All potential physical, psychological and social factors.

Non-medical interventions

- More time for oral/manual stimulation
- Increased communication between partners
- Sensual massage/warm bath
- Change of sexual routine
- Read appropriate literature e.g. Dr Rosie King's "Good Loving, Great Sex"

Recommendations for practice

Consider referral to psychological medicine services, such as Breast Cancer Clinical Psychology Services (RPH, FSH), or a Sex / Relationship Counsellor for further intervention.

Note: The use of testosterone/Viagra for sexual dysfunction is not supported by the evidence therefore is NOT recommended.

Bone loss

Recommendations for practice

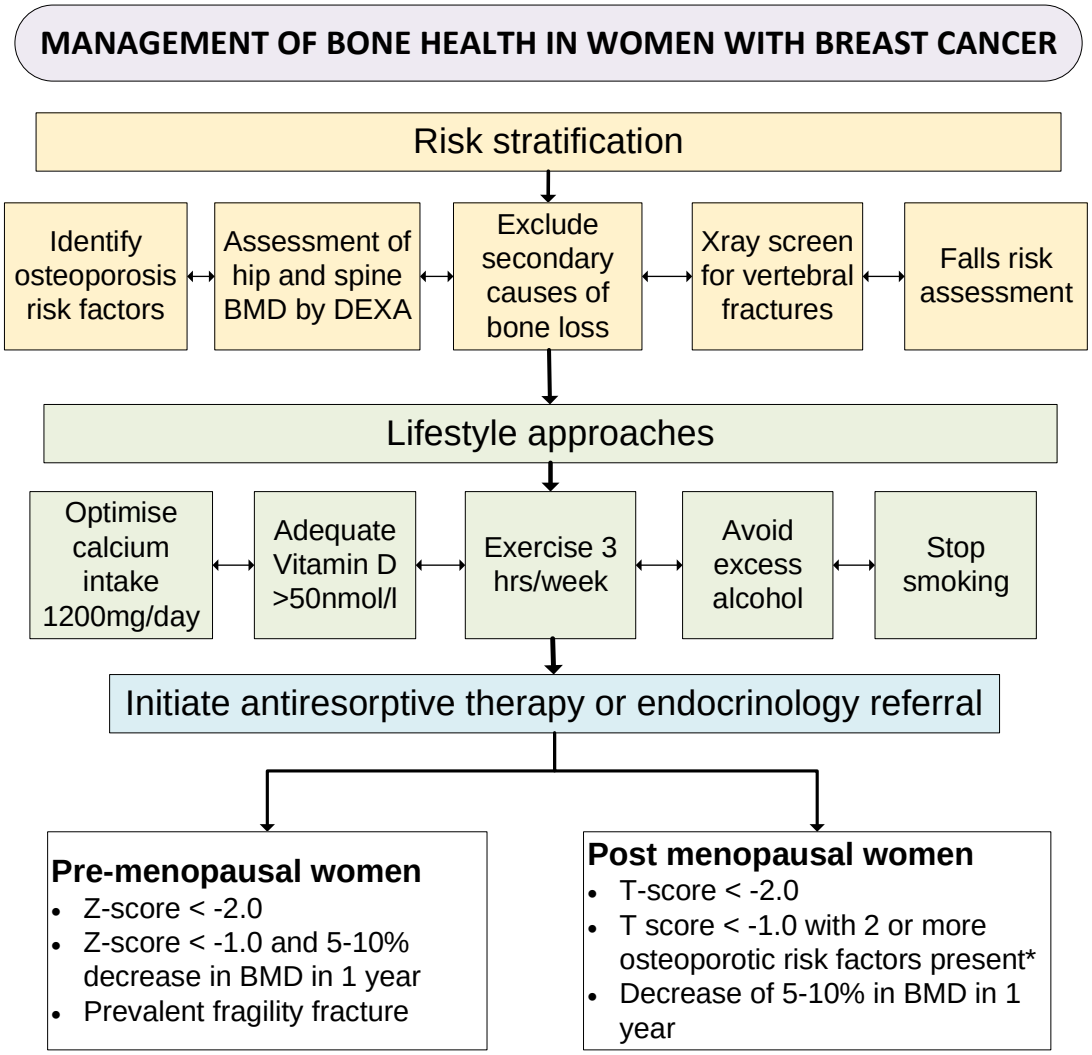
Consider bone densitometry (DEXA) in women:

- Following treatment for cancer with chemotherapy, ovarian suppression (or removal), Tamoxifen or Aromatase inhibitors
- With a personal or family history of osteoporosis
- With other risk factors for osteoporosis, such as, low BMI, smokers, malabsorption syndromes and corticosteroid or GnRH agonist use.

Provide the woman with information regarding:

- Calcium intake
  - Recommended daily intake of 1200mg / day
  - May require supplements if unable to have adequate dietary intake of calcium
- Adequate Vitamin D
  - Ensure adequate safe sunlight
  - May require supplementation
  - For further information, see KEMH Adult Medication Monograph: Colecalciferol (Cholecalciferol)
- Weight bearing exercises
  - Regular walking
  - Resistance / weights training
- Avoid smoking and excessive alcohol.

Bone loss flowchart[3]



Acknowledgment: Milat, F. & Vincent, A. (2015). Management of bone disease in women after breast cancer, Climacteric, 18:sup2, 47-55.

Abbreviations:

BMD:	Bone mineral density
BMI:	Body mass index
DEXA:	Dual-energy X-ray absorptiometry
FH:	Family history

Options for medication

Key points

1. The management of menopausal symptoms after breast cancer is best managed with a multidisciplinary approach.
2. Cancer Australia Clinical Practice Guidelines (2016) for breast cancer are available at www.canceraustralia.gov.au
3. Hormone therapy for women with a gynaecological cancer may be considered following advice from the treating Gynaecologic or Medical Oncologist

Indications for treatment

The treatment of menopausal symptoms following breast cancer should be based on:

- the severity of the symptoms and their impact on quality of life
- evidence for safety following breast cancer (if available)

Hormonal medications

1. Hormone replacement therapy (HRT) also known as Menopausal hormone therapy (MHT)

HRT containing estrogen is the most effective treatment for menopausal symptoms in healthy women.[4] The evidence suggests that HRT improves vasomotor symptoms, vaginal dryness and reduces the risk of fractures.

Unless hysterectomy has been performed, estrogen should be given in combination with progesterone to prevent an increased risk of endometrial hyperplasia or cancer.

In postmenopausal women, long-term use (greater than five years) of combined HRT (estrogen and progestogen) appears to increase the risk of breast cancer. This risk is **approximately eight additional new breast cancers per 10,000 women per year**.

Both estrogen only and combined HRT increase mammographic density, potentially reducing the efficacy of mammogram in detecting breast cancer and increasing the number of false positive recalls[5]. This effect is more pronounced with combined compared to estrogen only HRT.

Previous history of breast cancer and HRT

In women with a history of breast cancer, taking HRT appears to increase the risk of recurrence / or development of new breast cancers with a relative risk of 3.4. There is a lack of high quality research because of difficulty in recruiting for randomised controlled trials of HRT versus placebo.

The largest randomised control trial to address this question showed that, after a median follow up of 2.1 years, 14.9% of HRT users and 4.09% taking placebo had either a recurrence or development of a new breast cancer.[6]

Note:

It is not known whether the type or regimen of HRT and the estrogen/progesterone receptor status of the breast cancer have implications for the safety of use of HRT. Similarly, very little is known about the interaction between HRT and endocrine therapy for breast cancer. However, since endocrine therapy is essentially anti-estrogen, it is certainly possible that HRT may undermine the effects of endocrine therapy.

Recommendations for practice

- HRT should **not** be used as first line management for menopausal symptoms following breast cancer.
- Use of HRT may be justified to improve quality of life reasons when all other interventions have failed and the woman is clearly informed of the potential increased recurrence risk.
- HRT may be considered for women with metastatic disease where attainment of quality of life overrides all.
- HRT may be considered after some gynaecological cancers following discussion with Gynaecological or Medical Oncologist.
- For further information regarding products, dosing and administration, refer to KEMH Adult Medication Monograph: Estrogen (Oestrogen) HRT

2. Progestogens

High doses of progestogens have been used to treat advanced breast cancer. Progestogens at lower doses are effective in reducing menopausal hot flushes, but are not as effective as estrogen or estrogen and progestogen in combination.[7] A small study (2006) suggests that one dose of depomedroxyprogesterone acetate (DMPA) may also be effective[8].

The safety of progestogens for the treatment of menopausal symptoms following breast cancer is not known.

Recommendations for Practice

Progestogens are not recommended for the treatment of vasomotor symptoms as safety is uncertain and efficacy is likely to be less than that of estrogen and progestogen in combination, or estrogen alone.

3. Tibolone

Tibolone (Livial®) is a synthetic compound with weak estrogenic, progestogenic and androgenic properties. There have been no large studies assessing the impact of tibolone on the risk of breast cancer in healthy women. Tibolone does not appear to:

- stimulate breast cells in vivo
- increase mammographic density or increase the false positive recall rate for mammograms.

Tibolone has an unfavourable effect on serum cholesterol by reducing HDL cholesterol. While it has been known to improve bone density, its effect on fracture reduction is yet to be confirmed.

The researchers from the LIBERATE Trial (Organon) 2008, conclude “Tibolone increases the risk of recurrence in breast cancer patients, while relieving vasomotor symptoms and preventing bone loss”. Therefore the use of Tibolone for women with a known, past or suspected breast cancer will remain contraindicated.

4. Testosterone / Androgen Therapy

Testosterone may exert biological effects by acting directly on the androgen receptors or indirectly through conversion to estrogen by the aromatase enzyme. This mechanism is blocked by aromatase inhibitors. Levels of testosterone reduce gradually throughout adult life. Early or surgical menopause may be associated with a greater reduction in testosterone and its effects.

The Endocrine Society’s Clinical Guidelines recommend against making a diagnosis of androgen deficiency in women at this time because there is neither a well-defined clinical syndrome nor normative data on testosterone or free testosterone levels in women across their lifespan that can be used to define the disorder[9].

The safety or efficacy of testosterone supplementation following breast cancer is not known.

Recommendations for Practice

The generalised use of testosterone by women is NOT recommended because the indications are inadequate and evidence of safety in long term studies is lacking[9].

Non-hormonal medications

1.Gabapentin

Gabapentin is a gamma-aminobutyric analogue approved for the treatment of seizures and chronic pain. Use of 900mg per day has been found to be effective in reducing menopausal hot flushes for at least 12 weeks when compared to a placebo [10](Level 2).

Gabapentin’s use is limited by:

- side effects including somnolence and dizziness

Recommendations for Practice

- Gabapentin can be considered for treating hot flushes following breast cancer but women should be advised regarding cost (non-PBS), and potential side effects.

- **Recommend dose:** 900mg/ day in three divided doses.
  Start at 300mg daily - initial night time dosing is preferable due to possible excessive sleepiness and dizziness.
  Increase to 300mg three times a day over three to seven days.
  Gabapentin dosing should be tapered over a 1-week period when it is discontinued.

2. Clonidine

Clonidine is an alpha adrenergic agonist, which acts centrally to reduce vasoconstriction. Primarily used in the treatment of hypertension, clonidine has a modest effect in reducing hot flushes following breast cancer [11](Level 2).

It is poorly tolerated by some women who experience side effects of:

- constipation
- dry mouth
- drowsiness
- difficulty in sleeping.

Clonidine is approved by the PBS for the treatment of menopausal flushing in Australia.

Recommendations for Practice

- Clonidine can be considered for hot flushes following breast cancer but women should be warned about side effects.
- **Recommended Dose**: Oral, initially 25micrograms twice daily.
  Increase after two weeks to 50–75micrograms twice daily, if necessary.
  Clonidine is only available in the oral form in Australia.
- Stop if no benefit is noted after two to four weeks of treatment or if a woman experiences significant side effects.

3. Selective Serotonin / Noradrenaline Re-Uptake Inhibitors (SSRI / SNRI)

SSRI / SNRI are licensed in Australia for the treatment of depression.

The safety of **some** SSRI/SNRI in breast cancer women taking endocrine therapy is not known and they may interfere with the metabolism of Tamoxifen.

When co-prescription of Tamoxifen with an antidepressant is necessary, preference should be given to antidepressants that show little or no inhibition of CYP2D6 such as Venlafaxine.

Recommendations for Practice

- Women should be advised that the use of SSRI/SNRI may to be associated with anticholinergic side effects and that it may interfere with metabolism of Tamoxifen.[12]

- **Recommended Dose:** Venlafaxine slow release (SR) is started at 37.5mg once daily for a week.
  Increase up to 75mg once daily if well tolerated.
  Higher doses have not been shown to be useful for the treatment of hot flushes and may be associated with increased adverse reactions.
  Venlafaxine and SSRIs should be slowly tapered to minimise the occurrence of discontinuation symptoms. It is suggested to reduce dose over at least two weeks.

Non-hormonal medications

Most studies have only shown efficacy for 4-12 weeks durations. This is limited by the duration of the studies themselves. Benefits are often seen for longer periods of time, but response is an individual one.

What is the appropriate length of therapy?

Non-hormonal treatments for hot flushes appear to be effective in 1 to 2 weeks. If no clinical response is seen over this period treatment approaches should be modified.

The mean duration of hot flushes is around 5 years for spontaneous menopause.[13]

It is not known whether hot flushes after cancer treatment have a similar duration.

Patient information

See Menopause Service for medication patient information leaflets available.

References

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Resources

- The Women's Health Research Program. School of Public Health and Preventative Medicine. **A Practitioner's Toolkit for Managing the Menopause.** 2014
- Individual Patient Application (IPA) form

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