Empower – Menopause and Cancer Survivorship Pathway

Menopause and Cancer: What to Expect & Symptom Management

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Why is it important to know about Menopause Symptoms and Cancer?

- Some cancer therapies can affect the ability of the ovaries to produce eggs and hormones- Cancer therapies might **impair fertility & cause menopause-like symptoms**
- **Some patients are already suffering from (peri)menopausal symptoms before they start their cancer therapies**
- **Chemotherapy and pelvic radiotherapy** can result in a range of damage to the ovaries
- Targeted anti hormone therapies like **Zoladex and Tamoxifen and Aromatase Inhibitors** work by impeding the amounts or actions of **Estrogen** in the body.
- How you might feel on (or after) these therapies (as a result of estrogen fluctuations and/ or loss) may be more problematic for some than others- **but everyone should be aware of what might happen before they start their treatment**

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“Latrogenic Menopause”

- Evidence suggests that menopause caused by medical therapies may be **more severe and long lasting** than physiological menopause. Following a cancer diagnosis, women may be at an increased risk of affective disorders such as depression and anxiety and menopausal symptoms may exacerbate this risk[4, 5]

- Younger age at menopause may also be associated with psychological and sexual dysfunction as well as long term risks such as cardiovascular disease, osteoporosis and, potentially, cognitive dysfunction and dementia[6]

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Common Psychological symptoms of (Peri)Menopause

- Night sweat and hot flushes
- Menstrual Changes: heavier periods/ irregular periods
- Loss of Vaginal Elasticity & Lubrication
- Decrease in metabolism resulting in increase in weight
- Increase risk of metabolic syndrome
- Hair & skin changes
- Joint complaints
- Bladder complaints

Common Psychological symptoms of (Peri)Menopause

- Depression,
- Mood swings
- Anxiety
- Tiredness
- Memory loss
- Concentration loss
- Loss of libido
- PMS-type symptoms

So… what can be done ?

- Menopause hormone therapies (estrogen and progestagen and testosterone) aka HRT has become widely popular for the management of symptoms
- But what if you have been diagnosed with a Cancer?
- How might that affect your choices in managing menopausal symptoms?
- What are the recommendations from the experts? and
- Who can you turn to for ACCURATE information here in Ireland ?

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Firstly; what type of cancer have you been diagnosed with ?

- Your options and the safety of HRT use will generally vary depending on the **Cancer type with which you have been diagnosed**
- There are particular concerns about HRT use with **Sex Hormone Sensitive cancers** but
- As HRT is only lately been popularised & widely used, there will be very few studies looking directly at the pro's and con's of HRT use for (peri)menopause in people diagnosed with and treated for any malignancies

Common Cancers in Irish Females

- Skin (non melanoma)
- **Breast**
- Colorectal
- Lung
- Melanoma Skin Cancer
- Uterine **Lining** & Body
- **Ovary**
- Cervix
- Non Hodgkin's Lymphoma
- Stomach
- Kidney
- Mouth, Pharynx, Oesophagus
- Leukaemias
- Pancreas
- Brain
- Thyroid
- Hodgkin's Lymphoma

How is Guidance on HRT after cancer developed ? What do we know to be true?

How do we know anything to be **true** in medicine ?

Often we start with a question or hypothesis and start to gather data… but

- Data is not proof
- Data needs to be formulated, gathered, stored, analysed and interpreted before it can be converted into medical knowledge…

…and this can take decades !

So, what are the facts about Using HRT after Cancer ?

- No easy answers
- No quick fixes
- No guarantees

Common Cancers known to be Sex Hormone-linked

- Breast
- Ovary
- Womb lining

Consequences of Breast Cancer Treatments & Menopause symptoms

- **Surgery:** Oophorectomy will obv lead to immediate Menopause but even hysterectomy with ovary sparing is linked to early menopause symptoms – rarely mentioned
- **Chemotherapy:** any chemotherapy regimen can potentially lead to medical menopause but esp cyclophosphamide (Cytoxan)- and also when part of the CMF regime: cyclophosphamide, methotrexate, and fluorouracil. It may be temporary, but more likely to be permanent in older women
- Ovarian shut down with **Zoladex** will obv cause immediate Meno symptoms
- **Radiotherapy:** modern targeted treatments ***not usually linked to Meno symptoms***
- **Adjuvant Hormonal Therapy: Tamoxifen** may cause meno symptoms as can **Aromatase Inhibitors**; to a variable degree
- **Targeted Therapy**: **Trastuzumab** can cause many side effects including flushes

Adjuvant Therapies- AI's & Tamoxifen

- Adjuvant therapy medications eradicate dormant occult micro-metastases that may be in the lymph/ blood/ bone
- AI's stop other sex hormone in the blood from converting into oestrogen- they reduce **estrogen creation in fat** & are often given to people at medium to high risk of recurrence
- Tamoxifen blocks estrogen receptors – it is effective in both pre- and postmenopausal patients & has estrogen receptor **antagonist** activity in the breast.
- Oncologists report the use of these drugs has been the most significant contributor to the improvements in breast cancer survival*
- But both can cause lots of menopause symptoms esp muscle and joint pain and they impact the vagina in a variety of unpleasant ways so DISCONTINUAITON of adjuvant therapy is very common
- And… Tamoxifen use in post menopausal patients is liked to a small increased risk of endometrial cancer** – these drugs are useful but also problematic

How it should be done….

- In the UK, they recommend a written care plan should be developed at the end of active treatment (surgery, chemotherapy, Trastuzumab and radiotherapy)
- This care plan should be agreed with a NAMED doctor or nurse in the **Breast Clinic and a GP**
- It should include dates for review of adjuvant endocrine therapy for women with ER+ve cancer, details of mammograms **and information about signs and symptoms of recurrence, or treatment side effects, with contact details for immediate referral to specialist care or support services.**
- That information should include a **pathway for women experiencing estrogen deficiency symptoms arising from a natural or chemotherapy induced menopause, or to tamoxifen or aromatase inhibitor exposure.**

What about using HRT after a Breast Cancer Diagnosis ?

- There have been no large-scale, reliable studies where people with different types of breast cancer were enrolled according to their cancer type and then offered different types of HRT vs Placebo
- The belief in medical circles is that a such study would never get approval.
- In the absence of good clinical data, it is unlikely we will ever have a definitive guideline to advise on HRT use after breast cancer
- **It is generally not recommended to use systemic oestrogen or progestagen in someone with a diagnosis of breast cancer**

Using HRT after a Breast Cancer Diagnosis cntd.

- The BMS advises that a history of breast cancer should be considered a contraindication to systemic HRT. ‘Non-hormonal options should be the first-line treatment in women with a history of breast cancer, particularly those receiving tamoxifen or aromatase inhibitors’ is the current BMS advice.
- They say ‘people who have been diagnosed with BC who experience ongoing menopausal symptoms but who have failed to respond to non-hormonal management should be referred to discuss their options with a menopause specialist and oncology team.’
- An individualised plan based on the patient’s individual circumstances should be discussed.

What about local vaginal estrogen after a breast cancer diagnosis?

- Neither systemic HRT nor low dose, local vaginal oestrogen are recommended in women taking an **aromatase inhibitor** and with both, prescription should only take place after discussion between the patient, her primary health care and breast specialist team. We are often **given the green light** for LVE by one oncology service while told **"absolutely not"** by others!

- Local vaginal estrogen use **IS** supported by most oncologists for people with vaginal/ pelvic symptoms who are using **tamoxifen** if other, non – hormonal remedies have been unhelpful. Guidelines in both menopause and oncology support the use of LVE in people NOT USING AI's.

What about ER-/PR-/ HER2+ Breast Cancer?

- Iatrogenic menopause symptoms are not limited to women with hormone sensitive disease as **chemotherapy-induced ovarian suppression** will occur irrespective of the oestrogen receptor (ER) status of the primary tumour.[1]
- **HRT may not be without risk for those with an ER negative primary.**
- Although there is high concordance in hormone receptor status between first and second primary breast cancers**, a minority with an ER negative primary may present with an ER positive contralateral cancer (up to 30%)[2] and approximately 8% may present with ER positive metastatic disease.[3]**
- **There is generally less concern about systemic absorption from low and ultra-low dose vaginal oestrogen, which is minimal and could be acceptable where systemic therapy would not be.**

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What about HRT with BRCA mutations?

- Lifestyle and non-hormonal alternatives should be used as first-line management of vasomotor symptoms in women at very high risk of breast cancer (who are experiencing typical meno sx at the usual age) suggest the BMS
- But, they go on to say that '**HRT may be needed for severe, refractory symptoms and should be considered on an individual basis following specialist and patient discussion.'**
- *In the absence of data, it would be difficult to justify use of HRT for indications other than symptom relief, where longer duration therapy would be indicated as for example in population-risk women with POI. ???*

But it is a different story after Risk Reducing Surgery!

- The exception to this is BRCA1 and BRCA2 mutation carriers who have undergone risk reducing bilateral salpingo-oophorectomy (BSO).
- **Here, add-back HRT has not been shown to diminish the risk-reducing benefit of BSO on subsequent risk of breast cancer diagnosis (but clinical data is very limited**)
- Further studies are needed to clarify risk with combined compared with unopposed HRT and the optimal duration of use.
- **The current recommendation is that after risk-reducing BSO, add-back HRT is used until the age of an expected natural menopause (50/51),** after which non-hormonal alternatives are used as first-line management for symptom control and the prevention of chronic, oestrogen-deficiency health problems.

BMS is cautious but open

The British Menopause Society is guarded in its recommendations but emphasise individualisation of care. Their detailed guideline on managing menopause symptoms after a diagnosis of breast cancer includes:

- **Patients should be referred to a HCP with expertise in gynaecological endocrinology for counselling about the possible consequences of their breast cancer treatment BEFORE THE TREATMENT STARTS**
- Ideally, people diagnosed and treated for breast cancer should be encouraged to try **non-HRT strategies** but if these are ineffective,
- Systemic hormone replacement therapy or low-dose topical oestrogen may be considered, but only after taking **specialist advice**
- **Switching breast cancer hormone treatments or taking a break from them might also be suitable, but this needs to be discussed with the oncologist**

Ovarian Cancer- are not all the same

- Ovarian cancer is the fourth most commonly diagnosed cancer in females in Ireland with approx. 400 new diagnoses each year.
- **Use of HRT for > 5 yrs. risk may increase the risk of being diagnosed with ovarian cancer (WHI data)**
- There is no effective screening strategy for ovarian cancer. Investigation of symptoms includes TV USS, MRI and se CA125 measurement **but these are not to be used as screening tools.**
- Prevention- the only intervention proven to significantly reduce mortality due to ovarian cancer in women at high inherited risk of OC is risk-reducing bilateral salpingo-oophorectomy (RRBSO) - the possible outcomes of this surgery should be discussed with patients prior to surgery. While not inevitable, **it is not uncommon for patients to develop menopause symptoms after RRBSO- and may be at risk of premature/ early meno consequences**

Guidance on HRT will vary with ovarian cancer subtype

- For High grade Serous OC (75% of diagnoses), the available research suggests that it is reasonable to consider MHT.
- For Mucinous OC, which is not a hormone sensitive cancer, it is safe to consider MHT.
- For Clear cell OC, MHT may be considered but as this OC is linked to VTE, judicious choice of HRT dose, molecule and delivery is advised.
- For Germ cell OC, MHT can be offered if required.
- For Borderline OC (Slow growing, slow to spread, generally diagnosed at an early stage & usually cured by surgery). MHT can be offered if required.
- For Endometrioid OC; one of the more common OC's diagnosed in younger females, use of MHT appears safe but data is sparse
- For Low Grade Serous OC, which is highly hormonally driven and often managed by oestrogen blockers, use of MHT is not recommended.
- For Sex Cord Stromal tumours e.g. granulosa cell tumours, as these are usually hormone sensitive, use of MHT is not recommended.

HRT after Cancer

Should have

- Colorectal
- Vulval
- Vaginal

- Cervical
- Leukaemia
- Lymphoma

May have

- Endometrial
- Ovarian
  - High grade serous
  - Endometrioid
- Melanoma
- Lung

Should not have

- Breast
- Ovarian
  - Low grade serous
  - Clear cell
  - Sex cord stromal

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Endometrial Cancer*

- Currently, there is insufficient high-quality evidence to inform women considering HRT after treatment for endometrial cancer. The available evidence (both the single RCT and non-randomised evidence) **does not suggest significant harm, if HRT is used after surgical treatment for early-stage endometrial cancer.***
- Limited, very-low certainty, evidence suggests that HRT may have little or no effect on the risk of endometrial cancer returning for women who have been treated surgically for an early-stage endometrial cancer or their survival rates
- There is no information available regarding use of HRT in higher-stage endometrial cancer (FIGO stage II and above).
- The use of HRT after endometrial cancer treatment should be individualised, taking account of the woman's symptoms and preferences, and the uncertainty of evidence for and against HRT use.[1,2]

***not the rare 'endometrial sarcomas' which ARE estrogen sensitive & can be highly malignant* [3]**

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Vaginal and vulval cancer

- Since most vaginal/vulval cancers are squamous cell carcinomas, there is no evidence of recurrence of vulval disease with hormone use
- **HRT is not contraindicated.**

- Systemic and local vaginal oestrogen HRT can be offered after treatment for vaginal and vulval carcinoma.

Cervical Cancer

- **HRT is not contraindicated after treatment for squamous cell carcinoma of the cervix or adenocarcinoma of the cervix.**
- A systematic review of HRT and cervical cancer was published in 2021. Several studies linked significantly reduced risk of developing cervical squamous cell carcinoma in postmenopausal women treated with HRT, with a weak increase in the incidence of adenocarcinoma identified. There were no reports of a harmful effect of HRT on cervical cancer treatment outcomes.
- Several benefits (reduced metabolic risk, increased QoL) were identified in younger cervical cancer survivors especially.

Colorectal cancer

- **The WHI trial showed that the risk of colorectal cancer was reduced in the combined oestrogen and progestogen arm.**
- No effect was shown in the oestrogen alone group.
- The risk reduction of combined oestrogen and progestogen reduced after stopping HRT over 13 years cumulative follow-up.

HRT also considered OK after diagnosis of cancer of the ….

- Lung, Stomach, Kidney, Mouth, Pharynx, Oesophagus, Pancreas, Brain, Thyroid, Skin (non melanoma) & Uterine Body
- Hodgkin's & Non-Hodgkin's Lymphomas, Malignant melanomas & Leukaemias

What can be done about Menopause symptoms without HRT? What actually works ?

- Optimising general health & nutrition may help lessen some of the impact of the menopause **but will not replace benefits of HRT**
- **Some OTC supplements are advertised for menopausal symptom relief, but few studies show them to be more effective than placebo & they are not tested for safety**

Health Promotion: Diet

- Oily fish, low GI fruits & veg, whole grains, soya, legumes, etc all reduce LDL cholesterol
- Avoiding excess red meat & simple sugars can improve weight and reduce hot sweats
- **Vitamin D** intake of at least 400mIU/day will improve bone health – supplements will be advised in the winter
- **Calcium** 700-1200mg /day ideally via diet but supplements may be useful for people with low Ca diets

Health Promotion: Movement

Regular Physical Activity :

- Decreases premature death, heart disease, diabetes, high blood pressure, colon cancer, obesity and more
- Exercise has a beneficial effect on Bone & Muscle and can reduce the risk of falling by improving strength, flexibility & balance.
- Exercise improves most psychological symptoms
- Exercise reduces bad cholesterol and raises the good cholesterol

Health Promotion: Weight Gain Management

Menopause can result in weight gain due to:

- Metabolic slow down
- Shift from Gluteo- femoral to Central adipose deposition

Weight gain can trigger:

- **Tiredness & Low Mood which then promote increased calorie intake**
- **Overweight/Obesity is now thought of as a chronic medical illness as opposed to the result of poor lifestyle choices, new Rx interventions on trend**

Health Promotion: Reducing Alcohol

- Moderate alcohol intake (<2 units/day) is linked to lower mortality than abstinence – *although the link is unclear*
- **Breast Cancer risk however is higher in women who consume even low levels of alcohol (compared to abstinent women)**
- Heavy alcohol consumption is linked to increased rates of breast cancer, low bone density, falls & fractures and more

Health Promotion: Smoking Cessation (& vaping!)

<u>Not smoking:</u>

improves sleep, hair, skin & teeth quality

improves your exercise capacity, endurance & enjoyment

improves fertility for both men and women

increases your potential life span by 10-15 years

reduces your risk of Heart Disease, Emphysema, Lung Cancer, Throat Cancer, Mouth Cancer, Bladder Cancer, Breast Cancer, Thrombosis, Stomach Ulcers and more

<u>Stopping smoking:</u>

Reduces your risk of death from heart disease by 50% within 6 months

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Complimentary & Herbal Therapies

- Phyto Estrogens: have not been proven superior to placebo
- Isoflavones as found in Soya, Red Clover & Chick Peas, no evidence of relief
- **Lignans are found in Bran, Flax, Legumes and may give some benefit**
- **Herbal Remedies (all are probably safe for most women but not yet proven effective & NOT RECOMMNEDED WHILE ON ADJUVANT THERAPY)**
- e.g. Black Cohosh, Ginseng, EP oil, Dong Quai, Gingko biloba, Sage, Wild Yam & St John's Wort
- Vaginal interventions: moisturisers, lubricants, vaginal LASER rejuvenation may all have benefit
- "Bio Identical Hormones" is a marketing slogan- these products are created in compounding pharmacies that are often unregulated and **these products are not recommended for anyone but esp NOT after Breast Cancer**

Alternative Therapies: Flushes & Sweats reduce using CBT & Mindfulness

- **Cognitive Behavioural Therapy** has been found beneficial over placebo in several aspects of Peri menopausal management including **VMS relief with up to 50% reduction**
- **Access to CBT is not always easy and may be costly – try Sleepio and Silvercloud**
- Mindful Meditation Practice is recommended by NICE for help with low mood & anxiety (MENOS 2)

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‘Prescribables’ that might help YOUR Meno Sx

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Oxybutynin

- An anti cholinergic Over Active Bladder medicine, Oxybutynin has been shown to reduce severity & frequency of flushes/sweats at 2.5- 5mg two or three times a day – esp Daytime flushes
- *No license* for this as yet but being trialled in Breast Cancer survivors
- **Using it off label now in CMS, Holles St**

SSRI/ SNRI:

- One of the more effective pharmacologic alternatives to oestrogen includes the SSRI and SNRI classes. Their efficacy has been demonstrated in placebo-controlled trials and also a meta-analysis of 43 trials of non-oestrogen therapies.

- Those with statistically significant reductions in vasomotor symptoms in large, randomised, double blind, placebo-controlled trials of symptomatic women include paroxetine, escitalopram, citalopram, venlafaxine, and Desvenlafaxine.

- Obviously may help with low mood in higher doses, bad for libido though
- Reduction in hot flashes varies from 25% to 69%, with improvements in hot flash frequency and severity from 27% to 61%. Less consistent results have been seen with sertraline and fluoxetine.

Studies demonstrate efficacy with the following doses:

- venlafaxine 37.5mg titrated up to 150mg per day
- paroxetine 10 mg daily or
- citalopram 10mg-30mg
- Some SSRIs inhibit cytochrome P450 activity, an enzyme involved in tamoxifen metabolism and consequently most guidelines recommend that SSRIs such as fluoxetine and paroxetine must not be prescribed concomitantly with tamoxifen.
- **Venlafaxine** is the preferred treatment for women who are taking tamoxifen and has been shown to have a significant positive impact on VMS, mood and sleep

Gabapentin

- Although frequently used as an anti-epileptic or for relief from neuropathic pain- when given in high does- among other indications, gabapentin has also been shown to reduce vasomotor symptoms by as much as 50% in some women; esp good for night time flushes
- It can safely be used in women who are taking Tamoxifen. Due to its sedative effect, it may also benefit women who are reporting difficulty with sleep.
- **Gabapentin 100- 900 mg/day (typically administered three times per day) has been shown to be more effective than placebo in a number of trials.**
- The potential for side effects (headaches, dizziness, drowsiness) may limit its use, particularly in higher doses.
- A stepwise increase in dosage by 300 mg per week up to a maximum of 1.2 g is advised to minimise the side-effects.
- ***We use TINY doses in the CMS, Holles ST as it is a drug of addiction and has street value!***

Clonidine

- Clonidine is an alpha adrenergic receptor agonist and is **the only non-hormonal drug with a licensed indication for control of hot flushes**. Clonidine 25mcg is prescribed twice daily for two weeks, increased up to a maximum of 50 mcg three times a day.
- **Studies involving clonidine are small and results are mixed, suggesting a marginal benefit over placebo- which is frustrating for us as it is the only licensed alternative !**
- Side effects of clonidine are dose-related and at higher doses clonidine may cause sleep disturbance, dry mouth, and postural symptoms. It must be withdrawn gradually as abrupt cessation can cause rebound hypertension.
- It is not recommended as a first line treatment in women with no contraindication to HRT.

What seems to help/ what can be tolerated?

- **Flushes & Sweats:**

- SNRI/ SSRI (may get benefit from v low doses)*
- Oxybutynin (Kentara patch or 2.5mg PO going up slowly)
- CBT

- **Sleep**

- Gaba (start slow 100mg nocte and work up to 300mg TID) or Pregabalin (50-300mg daily in div doses)
- Mirtazapine 7.5mg nocte
- Phenergan 25mg nocte/ Piriton 4mg nocte
- Sleepio app

- **Mood**

-SNRI/ SSRI: Sertraline best for anxiety*

-CBT

- **Joint pains**

-Yoga/ Acupuncture

-Gaba (as above)

- **GSM**

-Moisturisers/ Lubes

-Local Vag E2 or E3 (C/I w AI)

-LASER??

Avoid Paroxetine, Fluoxetine and Sertraline for Tamox users- try them on Venlafaxine, Citalopram or ?? D/W Oncology and try a change to AI)

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OTC alternatives

Phytoestrogens and Herbal remedies

- Isoflavones and phytoestrogens (nonsteroidal compounds that occur naturally in many plants, fruits, and vegetables) have not been consistently found to be more efficacious than placebo for vasomotor symptoms. Data from some of the better researched phytoestrogen containing preparations/ supplements appear to demonstrate some benefits, not only for symptom relief, but also on the skeleton and cardiovascular system.
- A meta-analysis of soy isoflavones showed a 25% reduction in hot flushes after elimination of the placebo effect.
- Data regarding long-term health outcomes such as ischemic heart disease, osteoporosis or endometrial safety are not available.
- **Phytoestrogens and black cohosh are considered contraindicated in women with a history of an oestrogen-sensitive cancer.**
- St. John's Wort can affect the efficacy of warfarin and other conventional medicines.
- **There is also concern that it could potentially affect the metabolism of Tamoxifen**

Acupuncture

- Acupuncture is one of the most common complementary therapies for vasomotor symptoms
- The evidence for its efficacy is conflicting
- Most of the trials have been small and may have methodological flaws
- A randomised, sham-controlled (placebo) trial in 327 peri- or postmenopausal women who reported moderate to severe VMS. The patients were randomly assigned to 10 acupuncture (or sham acupuncture) treatments over two months
- The reported severity and frequency of vasomotor symptoms after treatment was reduced by equal amounts in both interventions. However, other double-blinded trials have found some benefit of acupuncture over sham-acupuncture
- More trials are needed to clarify

Joint and Musculoskeletal symptoms are linked to cancer treatments

- Musculoskeletal symptoms associated with the use of aromatase inhibitors is estimated to affect just under one half of treated women- they usually develop **within a few months of commencing treatment and they may persist for the duration of use.**
- Common symptoms include morning stiffness and pain affecting the hands, knees, hips, lower back, and shoulders- t**hese most likely result from estrogen deprivation but inflammatory pathways and a tenosynovitis type effect (fluid retention in joints) may also have a role in the cause**

Non-Medical therapies for Joint pains include:

- **Aerobic exercise** and resistance training -improves pain symptoms and muscle strength
- **Yoga** improves muscle and joint pain (myalgia and arthralgia)
- **Acupuncture** has also been reported to be of benefit in reducing pain too
- **Weight** management

Medical therapies for Joint pains include:

- SNRI (duloxetine), oral testosterone, diuretics and omega-3 fatty acid have all shown some improvement but
- Most of these studies are of a short duration (less than 6 months) and further longer-term, controlled evaluation is required to determine efficacy and side-effect profiles.
- The use of oral testosterone (i.e. 40mg or 80 mg of testosterone undecanoate) was not associated with any increase in serum estradiol when compared to women allocated placebo)*
- Uncontrolled data suggests that **Bisphosphonates** may reduce aromatase-induced arthralgia, in addition to preventing bone loss.
- **Switching between aromatase inhibitors (i.e. letrozole and anastrozole) and intermittent letrozole dosing are further areas of current investigation.**

The specialist authority for menopause & post reproductive health

BMS British Menopause Society

Prescribable alternatives to HRT

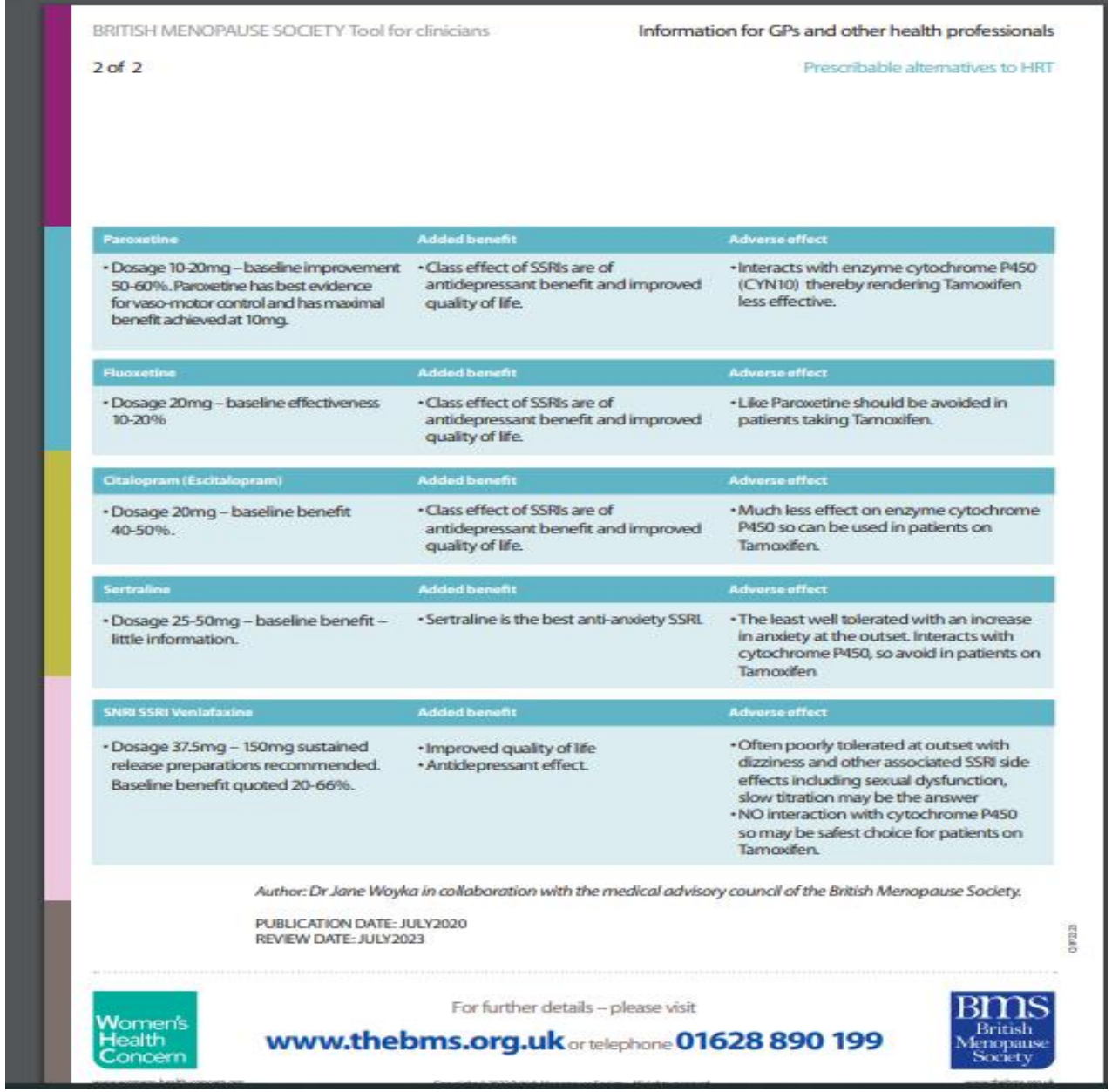
Introduction:
Most prescribable alternative therapies have been evaluated for their impact on vaso-motor symptoms. Some of them also have an impact on mood and well-being. The class effect of the drug is important in selecting what is likely to be the best alternative for your patient. Menopause treatments also tend to have a high placebo response often as great as 50% which may enhance quoted "baseline effectiveness".

Gabapentin	Added benefit	Adverse effect
• Gamma amino-butyric acid analogue used to treat epilepsy, neurogenic pain and migraine; reduces hot flushes at a dose of 900mg per day in about 50% of patients.	• Improved quality of sleep • Reduced pain.	• Dry mouth dizziness and drowsiness with a very specific dose related component • Patients will find their own level • Weight gain • Schedule 2 controlled drug.

Pregabalin	Added benefit	Adverse effect
• Dosage 50-300mg in divided doses • Baseline improvement similar to Gabapentin.	• Improved quality of life and note now Pregabalin is used as an antidepressant.	• Similar to Gabapentin but less marked and therefore better tolerated • More expensive • Schedule 2 controlled drug.

Clonidine	Added benefit	Adverse effect
• Dosage 25-50 micrograms bd up to a maximum of 75 micrograms bd or 50mcg tds.	• May complement other anti-hypertensive drugs • Only licensed option.	• Interaction with anti-hypertensive drugs and not suitable for patients with baseline low blood pressure • Must be reduced gradually otherwise causes rebound hypertension • Dose related side-effects include sleep disturbance in at least 50% of patients, dry mouth nausea and fatigue.

SSRI - Antidepressants	Added benefit	Adverse effect
• In general baseline effectiveness 20-50%.	• Class effect of SSRIs are of antidepressant benefit and improved quality of life.	• Class effect of SSRIs include initial side effects such as nausea, dizziness, short-term aggravation of base-line anxiety and mood, so encourage your patient to persevere and if necessary take on alternative days, even ½ tablet • Class effect of all SSRIs is sexual dysfunction • No one SSRI is better than any other in this respect and there is great individual variation in response.



BRITISH MENOPAUSE SOCIETY Tool for clinicians

Information for GPs and other health professionals

2 of 2

Prescribable alternatives to HRT

Paroxetine	Added benefit	Adverse effect
• Dosage 10-20mg – baseline improvement 50-60%. Paroxetine has best evidence for vaso-motor control and has maximal benefit achieved at 10mg.	• Class effect of SSRIs are of antidepressant benefit and improved quality of life.	• Interacts with enzyme cytochrome P450 (CYN10) thereby rendering Tamoxifen less effective.
Fluoxetine	**Added benefit**	**Adverse effect**
• Dosage 20mg – baseline effectiveness 10-20%	• Class effect of SSRIs are of antidepressant benefit and improved quality of life.	• Like Paroxetine should be avoided in patients taking Tamoxifen.
Citalopram (Escitalopram)	**Added benefit**	**Adverse effect**
• Dosage 20mg – baseline benefit 40-50%.	• Class effect of SSRIs are of antidepressant benefit and improved quality of life.	• Much less effect on enzyme cytochrome P450 so can be used in patients on Tamoxifen.
Sertraline	**Added benefit**	**Adverse effect**
• Dosage 25-50mg – baseline benefit – little information.	• Sertraline is the best anti-anxiety SSRI.	• The least well tolerated with an increase in anxiety at the outset. Interacts with cytochrome P450, so avoid in patients on Tamoxifen
SNRI SSRI Venlafaxine	**Added benefit**	**Adverse effect**
• Dosage 37.5mg – 150mg sustained release preparations recommended. Baseline benefit quoted 20-66%.	• Improved quality of life • Antidepressant effect.	• Often poorly tolerated at outset with dizziness and other associated SSRI side effects including sexual dysfunction, slow titration may be the answer • NO interaction with cytochrome P450 so may be safest choice for patients on Tamoxifen.

Author: Dr Jane Woyka in collaboration with the medical advisory council of the British Menopause Society.

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Women's Health Concern

For further details – please visit

www.thebms.org.uk or telephone **01628 890 199**

BMS British Menopause Society

What about Osteoporosis?

- Osteoporosis is prevented by HRT- it slows down the bone loss that is a natural consequence of the menopause
- **Preventing Osteoporosis via HRT is a major additional benefit for menopausal women who use HRT for the treatment of their menopause symptoms or who have had BSO**
- There is no evidence that any other alternative treatment for menopause symptoms are beneficial for osteoporosis prevention but the benefit of HRT on OP is quickly lost when HRT is stopped so another therapy must be offered
- **Bisphosphonates** may reduce bone recurrence and **breast cancer mortality** in postmenopausal women with early-stage disease and is offered to postmenopausal women with lymph node involvement (considered in people without nodal involvement but considered at high risk of recurrence) *

New options for flushes on the horizon

- **'Fezolinetant'** is the first of the new Selective Neurokinin-3 Receptor Antagonists to come to market
- Improvements in hot flush frequency, severity, and quality of life has been shown in US and European clinical trials using NK3R antagonists in postmenopausal women
- How do they work?? Well, flushes start in the brain. Nerve cells is the brain (KNDY Neurons) rely on Estrogen to stay balanced in calm.
- In the absence of E, those neurons become hyperactive releasing transmitter chemicals that mess up your body's ability to regulate temperature. The NK3RA's BLOCK those neurons and reduce the flushes

‘Oasis 4’ trials in Ireland[1]

- Elinzanetant is another NK3/4 inhibitor being developed
- There is a trial recruiting in Ireland right now to see how useful it is in treating vasomotor symptoms (VMS) in women with hormone receptor positive breast cancer on anti-endocrine therapy.
- The primary end points of the study will be mean changes in frequency of hot flushes at 4 and 12 weeks.
- At randomisation patients will receive either Elinzanetant or placebo for 12 weeks and after they all patients will receive Elinzanetant for 40 weeks
- They will then have the option to enrol on a follow-up study to access the drug for another 2 years.

OASIS stands for ‘Outcome and Assessment Information Set’

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GENITO-URINARY SYNDROME of the MENOPAUSE or “GSM”

Is the new term for vulvo-vaginal atrophy & describes the group of menopausal symptoms and signs including:

- **Vaginal dryness**
- **Vaginal burning & irritation**
- **Sexual symptoms such as lack of lubrication &**
- **Dyspareunia (painful sex) &**
- **Urinary symptoms such as:**
- **Urgency, Frequency, Dysuria & recurrent Urinary tract Infections**

GSM is a consequence of Estrogen deficiency:

Loss of Estrogen causes a reduction in the number and quality of blood vessels in the pelvis is reduced) & Thinning of both muscles and vaginal lining epithelium (with an increase in fat deposition) resulting in…

- **Vaginal Dryness**
- **Dyspareunia- painful sex**
- **Altered pH with a resultant increase potential for BV and other infections**
- **Traumatic bleeding, after penetration & after PV exams**
- **Urinary Incontinence (urge, frequency & mixed) & more Frequent UTI's.**
- **Linked to Pelvic Floor Prolapse as well**

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Impact on Sexuality

- For some the Menopause Transition coincides with a disimprovement in Sexuality & Sexual function
- **Low libido & Lack of orgasmic sensitivity may be reported**
- Is this a direct consequence of falling sex hormones or social influences or both ?
- **What is the role of testosterone replacement?**

Treatments for GSM

- Medical OTC
- Medical Rx
- Non medical

Medical treatments: OTC

- Vaginal moisturisers maintain vaginal hydration, Long-term relief of vaginal dryness, decrease pH to premenopausal levels but **do not improve epithelium (try Replens, Regelle, Multi-gyn, Yes, etc.)**

- Vaginal lubricants provide a **temporary moistened vaginal epithelium**. May be water, silicone or oil based (KY, Sylk, Yes, etc. etc.) Herbal remedies (soy, black cohosh, etc) not effective over placebo **acc to 2008 'HALT' study**

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GSM:
Medical Treatment Options: LVE

- Local vaginal estrogen (LVE) in the form of ESTRIOL (E3) (Imvaggis, Ovestin) OR Estradiol (E2) will thicken the epithelium, decrease dryness, return vaginal pH to normal and improve microflora with fewer UTI and decreased OAB symptoms
- Adherence issues; studies suggest just 50- 70% take as recommended!
- **4- 6 months to see full results - so perseverance**
- **Dosing in MIMS is inaccurate**
- **New Blissel will be avail soon**

What about LVE for people on Adjuvant Therapies?

- LVE can be considered in women who have estrogen negative tumours or who are taking tamoxifen, it should be discussed with the relevant oncology team
- LVE should not be used in women taking aromatase inhibitors.
- Ospemifene is licensed for use in women who have completed their breast cancer therapy. But there is limited long-term safety data from clinical trials so it is best to inform the breast specialist team in advance.
- Due to a lack of long-term data, NICE recommends laser therapy should only be used in the context of a clinical trial
- Vaginal DHEA ("IntraRosa") acts locally and seems to be effective even when used with tamoxifen and aromatase inhibitors.
- Systemic absorption is meant to be minimal, but clinical trial evidence about the safety and efficacy of DHEA is required in women treated for breast cancer
- **The American Society of Clinical Oncology Clinical Practice Guidelines states that DHEA can be offered to women with current or a history of breast cancer who have not responded to other treatments !**

DHEA (de hydro epi-androsterone)- a vaginal cream –Prasterone (“IntraRosa”)

- Aromatisation of androstenedione and testosterone locally to estrone (E1) and estradiol (E2)
- Works mainly intra cellularly and so **virtually NO systemic exposure**
- Vaginal inserts 6.5mg (0.5% formulation)
- **May be preferred in breast CA women but no guidelines as yet and still not recommended**
- Common reactions / side-effects: Vaginal discharge

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Ospemifene: a pill you swallow for your vagina

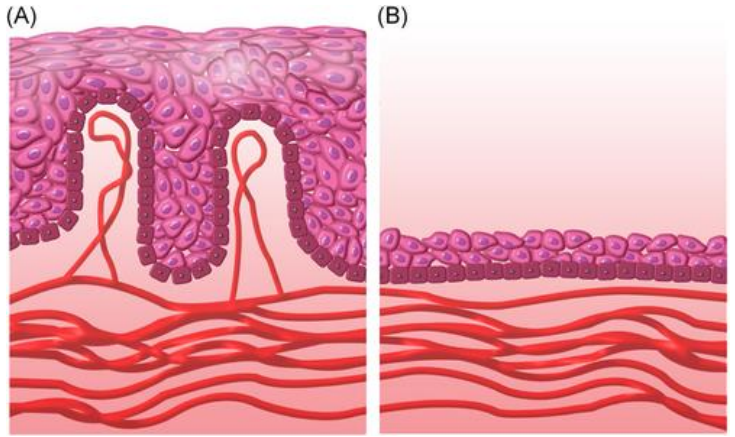
- **Selective Estrogen Receptor Modulator known as** Ospemifene is an oral selective oestrogen receptor modulator (SERM).
- It acts as an oestrogen agonist in the vaginal mucosa, lowering the vaginal pH and improving sx such as vaginal dryness and dyspareunia. It acts as an oestrogen antagonist on the endometrium and breast tissue. It may precipitate or worsen VMS.
- A 60 mg daily dose is available on prescription and holds a European license under the name ‘Senshio’.
- It is available on order in the ROI but not covered by the medical card or DPS.
- Some sources say ospemifene may be used in women with a history of breast and endometrial cancer who have completed treatment (there is no clinical trial data for patients with current breast cancer). It is not yet licensed for this use in Ireland.
- The 2019 BMS consensus statement on use of MHT in women diagnosed with breast cancer stated: “Ospemifene should not be prescribed to women with a history of breast cancer.”

GSM after Breast Cancer

- **Very common side effect of the cancer therapy**
- Vaginal estrogen Generally regarded as safe **regardless of receptor status**
- **No evidence of associated recurrence – ever**
- Concerns about patients on AI's thanks to a small, badly controlled 2006 study
- **BMS suggests offering non-E remedies first and then local vaginal estrogen if oncology do not have an objection**

Non-medical treatments for GSM

- Sexual activity
- Vibrators, dilators
- LASER rejuvenation (Mona Lisa, Fotona)



Resources

- www.primarycarewomenshealthforum.org
- www.thebms.uk
- www.womens-health-concern.org
- www.menopausematters.co.uk
- www.patientinfolibrary.royalmarsden.nhs.uk/brca1brac2

Thank you!