Management of Menopausal Symptoms

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Menopausal Symptoms After a Diagnosis of Breast Cancer

- Prevalence E2 deficiency symptoms after breast cancer +/- 80-95%
- More common if < 50 yrs

Management of menopausal symptoms is crucial:

- Affects of QOL
- Adherence +/- 40% women do not adhere to ETx
  - Adherence < 80% planned dose reduces TTR by 50%

- Hot Flushes
- Urogenital Symptoms
- Sexual Dysfunction
- Musculoskeletal Symptoms
- Cognitive Impairment
- Fatigue
- Weight Gain
- Depression and anxiety

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Howard-Anderson et al., JNCI 2012

What are the risks of HRT after a Breast Cancer Diagnosis?

	HABITS	STOCKHOLM	LIBERATE
n	442 (898)	378 (884)	3148
HRT	Estradiol +/- norethisterone	Estradiol +/- medroxyprogesterone acetate	Tibolone
ETx allowed	Tamoxifen	Tamoxifen	Tamoxifen or AI
HR	2.4	HR 0.82	HR 1.4

Most guidelines state HRT contraindicated after breast cancer

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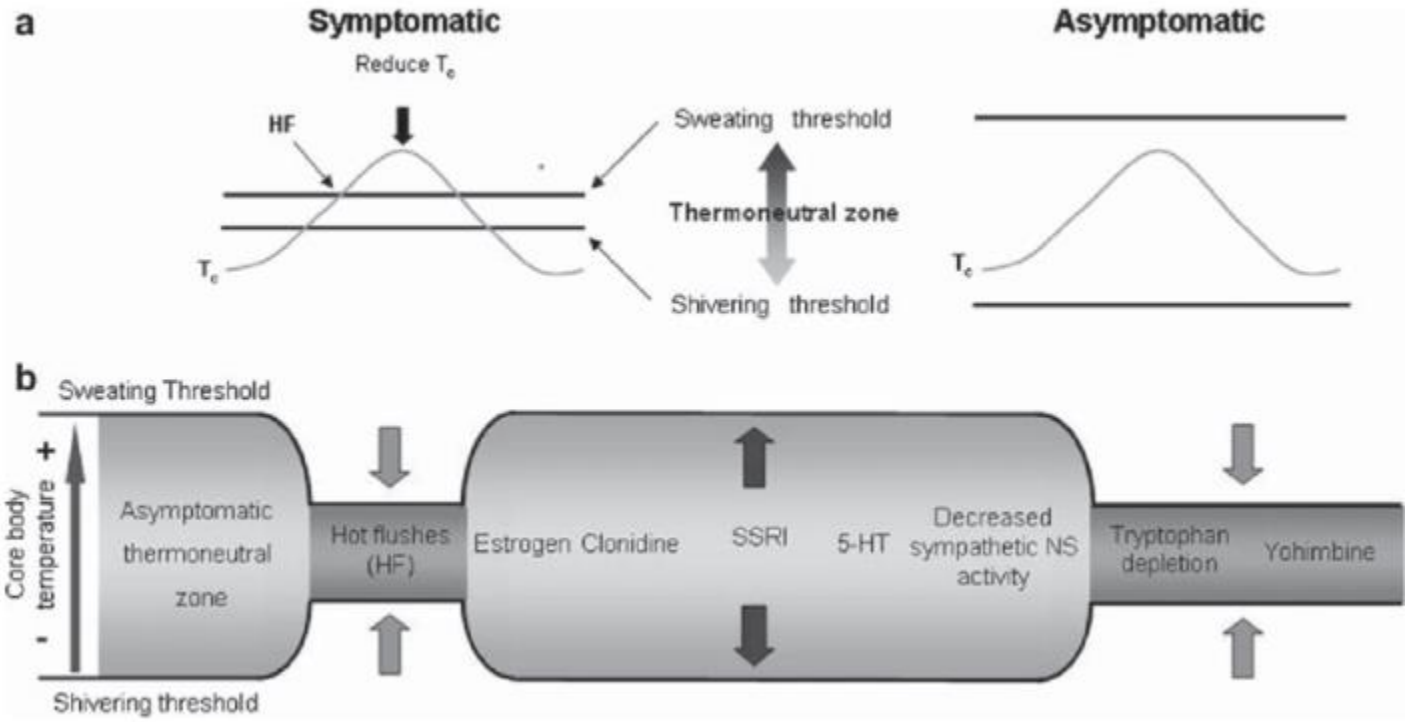
Vasomotor Symptoms (VMS)
Why Do Women Get Hot Flushes?



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Freedman et al., 2016

VMS: Self Help and What to Avoid

Lifestyle Changes

- Cooling techniques
  - eg layers, natural fibres
- Avoid triggers eg alcohol, spicy foods
- Weight Loss
- Exercise

Agents with no proven activity against Hot Flushes

- Vitamin E – no benefit v placebo
- Evening primrose oil- most trials no better than placebo
- Magnets

Phytoestrogens

- Black Cohosh
- Red Clover
- Soy

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Interventions for VMS

Data Interpretation complicated by:

- Differences in study populations
- Variation in outcome measures
  - Frequency (objectively and subjectively)
  - Frequency x severity scores
- Lack of head to head comparisons
- Underpowered trials
- Short term –often 12 weeks

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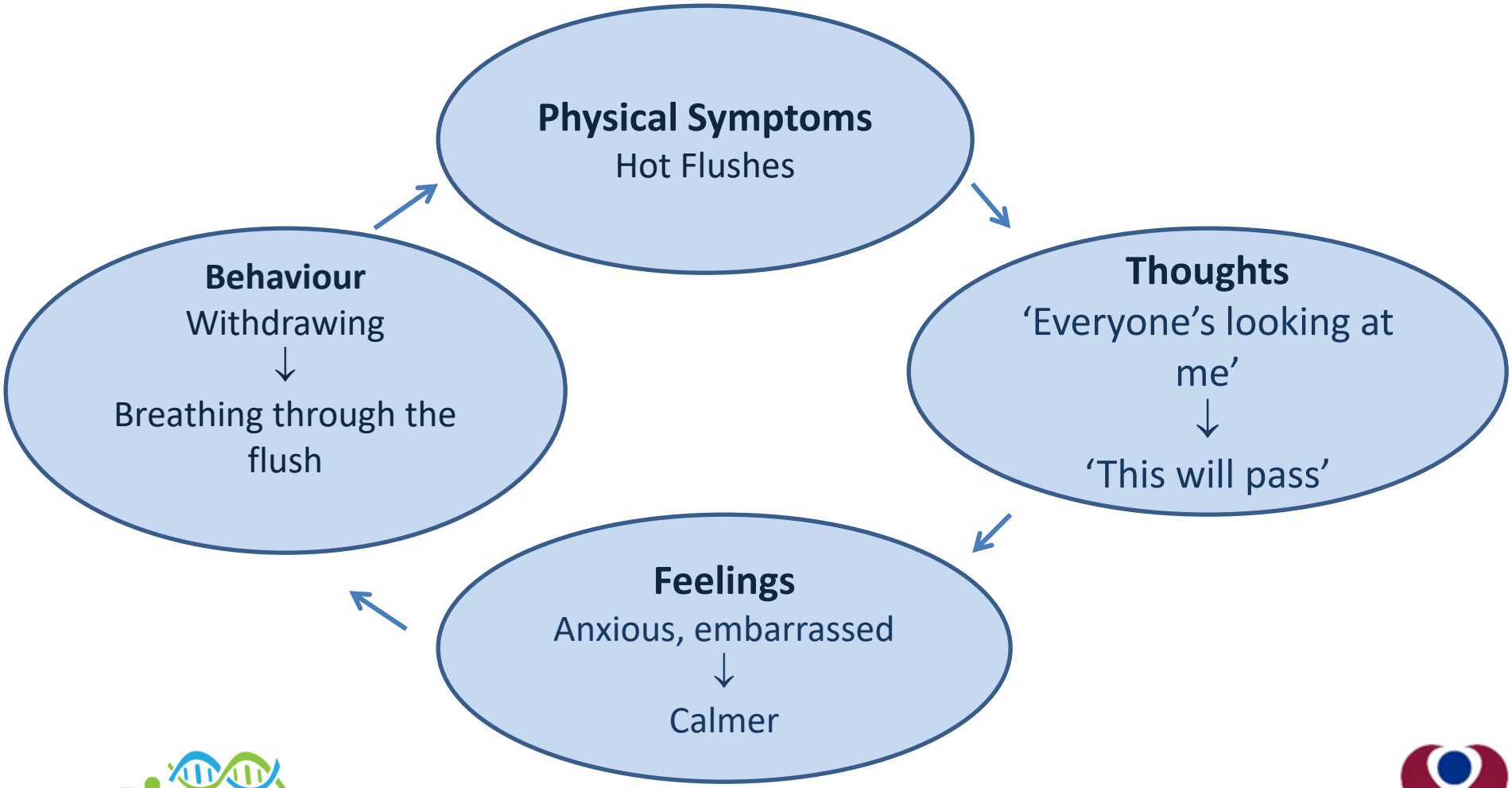
Cognitive Behavioural Therapy for VMS



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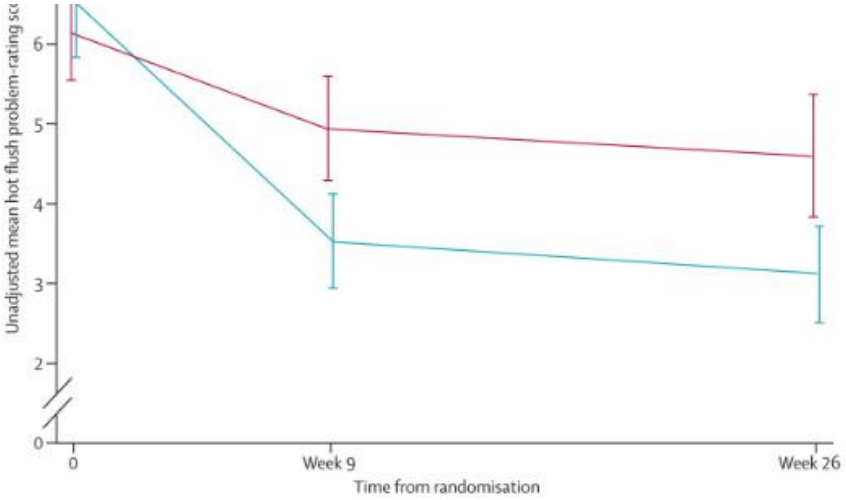
Cognitive Behavioural Therapy for VMS: MENOS1 Trial

RCT (n=96) ♀ w Breast Cancer

Group CBT 90min/wk for 6wks

v

usual care



Results

- CBT ↓HFNS problem rating p<0.0001
- Benefits:
  - maintained at 6/12
  - also seen in mood and sleep
- ↓ frequency of HF ~38% across both groups
- Recommended by North American Menopause Society

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Mann et al., 2012

Acupuncture for VMS

- Cochrane review 2013
  - Acupuncture better than no intervention ↓ severity / frequency HF
  - Better than sham at ↓ severity but not frequency HF
- 2 RCT in ♀ with breast cancer
  - Acupuncture vs venlafaxine / acupuncture vs gabapentin
  - both ↓ HF frequency and severity
  - More sustained response to acupuncture in both studies
  - Less adverse events with acupuncture
- Royal Marsden audit – 80% get ↓ 50% HF with self needling approaches allowing therapy for up to 6 years

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Dodin et al., 2013; Walker et al., 2010; Mao et al., 2015; Filshie et al., 2005

Pharmacological Interventions for VMS (1) Selective Serotonin Reuptake Inhibitors (SSRIs) & Serotonin-norepinephrine reuptake inhibitors (SNRIs)

- RCT demonstrate efficacy of SSRIs (eg paroxetine, citalopram) and SNRIs (eg venlafaxine) across breast / non breast cancer

Efficacy

- Overall 70-80% reduction in hot flash number and severity
  - Placebo effect of +/- 30%
- Symptom improvements occur 1-2/52

Dose Response

- Citalopram- efficacy and s/e = 10/20/30mg
- Paroxetine – 10mg=20mg; more AEs with 20mg
- Venlafaxine 150mg = 75mg > 25mg; more AEs with 150mg
- Start drugs at lower dose

Fluoxetine and Paroxetine should be avoided on Tamoxifen

Johns C et al., 2016

Pharmacological Interventions for VMS (2): Oxybutynin for hot flushes in women unable to have hormone therapy

RCT (n=150)

Inclusion Criteria

- 28 hot flushes /week for >1/12; 62% AI or tamoxifen
- Placebo v Oxy2.5mg bd v Oxy5mg bd for 6/52

Results

- ↓Hot flush frequency: 2.6 v 4.8 v 7.5
- HFS -5.1 v -10 v -16.2

RCT against venlafaxine, for a longer duration funded

Side effects : dry mouth, may cause cognitive issues in elderly

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Leon-Ferre et al., SABCS 2018

Pharmacological Interventions for VMS Gabapentin and Pregabalin

- Gabapentin / pregabalin- licence for epilepsy / neuropathic pain

- **RCT (n=371)**
  - Placebo v Gabapentin 100mg tds v 300 mg tds
  - 300mg tds ↓ HF more effective than placebo (15% vs 31% vs 46%)

- **RCT (n=163)**
  - Placebo v Pregabalin 75 mg bd vs 150 mg bd
  - Both doses ↓ HF: 75mg more tolerable (50% vs 65% vs 71%)

Side Effects: somnolence, fatigue

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Pandya et al., 2005; Loprinzi et al., 2010

Pharmacological Interventions for VMS: Clonidine

- Clonidine: α-2 adrenergic agonist anti-hypertensive
- UK licence for non-hormonal management HF

3 RCTs:

- Venlafaxine 75mg vs clonidine 0.1/0.15mg po
- 1 study (n=80) venlafaxine more effective; 2 other equivalent
- Time to onset of HF reduction faster with venlafaxine
- 1 study – AES to venlafaxine commonest reason to stop

Side effects Clonidine: hypotension, dry mouth, fatigue
Venlafaxine: anorexia, nausea, constipation, reduced libido

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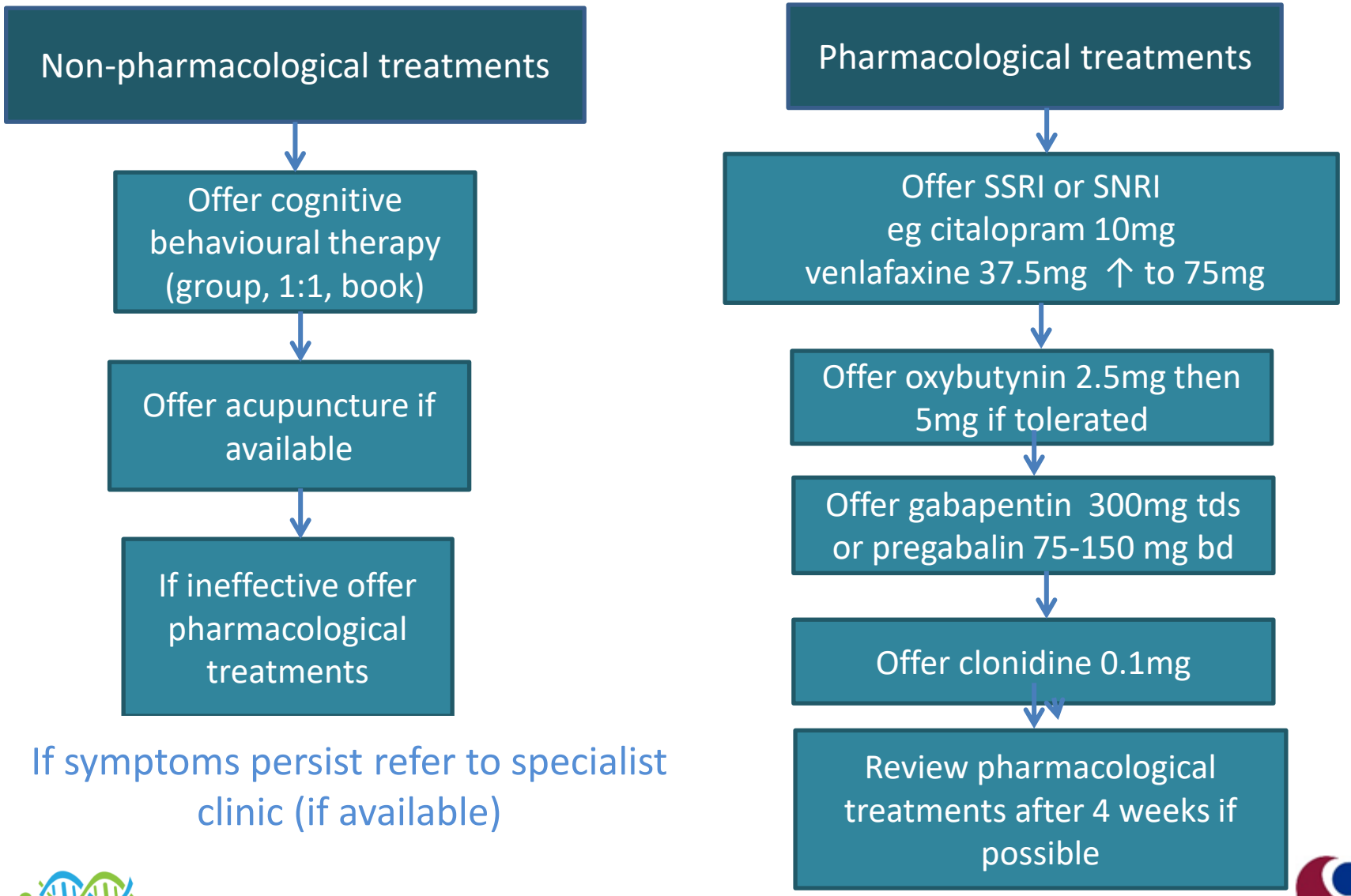
Loibl et al., Ann Oncol 2007; Buijs et al., 2009, Boekhout et al., 2011

Management of VMS



If symptoms persist refer to specialist clinic (if available)

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Genitourinary syndrome of the menopause (GSM)

- Common (?70% ♀ on ETx) and likely under-reported
- ↓E2 →thinning of urogenital tissues

- Variety of symptoms including:
  - Dryness /burning/ itching
  - Urinary frequency / recurrent UTIs
  - Pain and discomfort during sex

- Scoring systems are poor, often focusing on sexual activity
- Profound E2 deprivation caused by AI worsens GSM

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Management of GSM

- Smoking Cessation
- Avoid fragrances soaps, feminine hygiene products
- Pelvic floor exercises
- Maintain sexual actively if possible
- Vaginal lubricants
  - Short term lubrication only
  - Eg Sylk, Yes
- Vaginal Moisturisers
  - Used long term to deliver moisture and maintain physiological vaginal pH
  - Effects last +/- 72hrs; may take 30 days to notice improvement
  - Eg Hyalofemme, Replens

Are Vaginal Estrogen (VE) Safe After Breast Cancer?

- Vaginal moisturisers relieve symptoms but do not reverse atrophy
  - VE is superior to Replens or placebo in ♀ w GSM
  - Replens is not superior to placebo in breast cancer survivors
- Vaginal estrogen most effective intervention for GSM
- In ♀ +/- Ca Breast - systemic absorption seen w (higher doses) VE
- For women on AIs small rises may impact on AI efficacy
- Retrospective do not appear to show increased recurrence risk with VE
- Small, short term studies (+/- 12 weeks) in women on AIs suggest minimal absorption with low dose preparations eg:
  - Vagifem 10mcg (estradiol)
  - Estriol 0.005% vaginal gel

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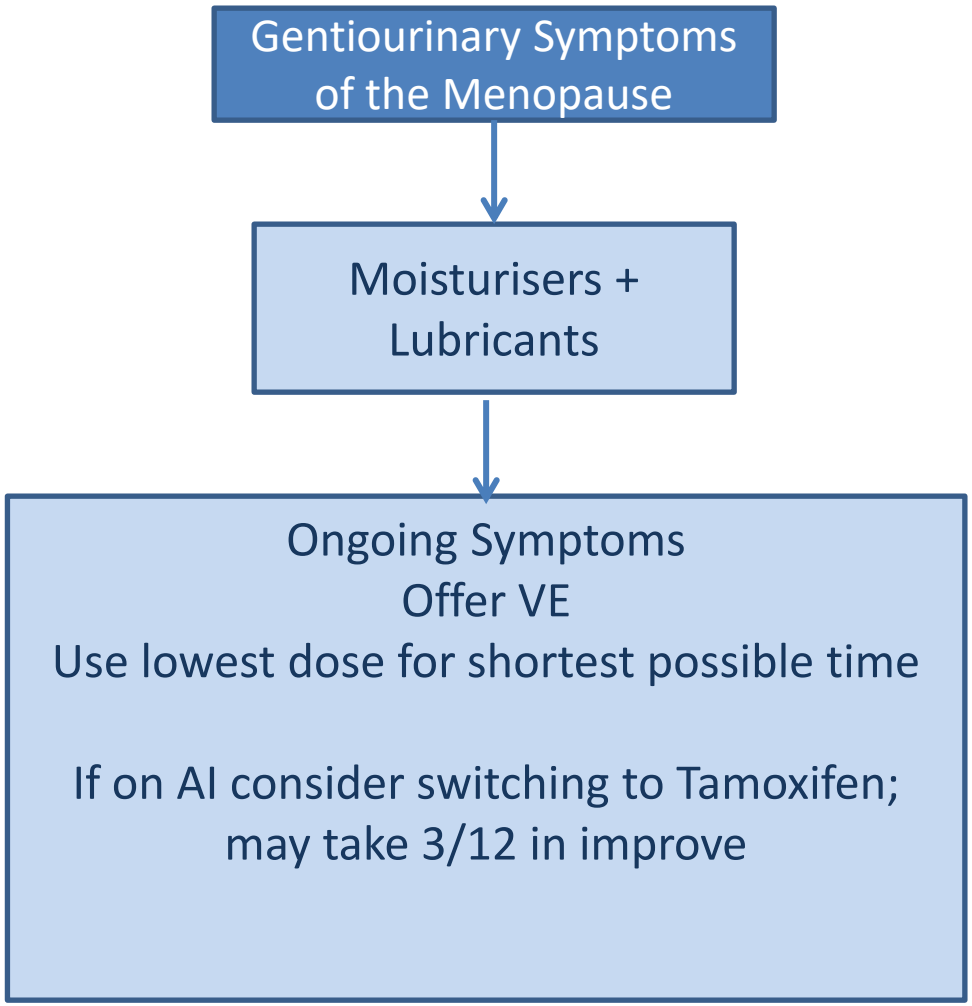
Bygdeman M et al., 1996; Loprinzi et al., 1997; Le Ray et al., 2012 Melisko et al., JAMA Oncol 2017

Management of Genitourinary Symptoms of the Menopause



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Aromatase Inhibitor Induced Arthalgia

- Arthralgia – more frequent after the menopause
- More common after chemotherapy < tamoxifen < Ais
- Reported in 50-80% women taking AI
- Aetiology of AI associated arthalgia uncertain, E2 deprivation +/- activation of inflammatory pathways
- Develops soon after commencing treatment and may persist for duration of treatment
- Generally improves after 2 weeks discontinuation

Management of Aromatase-Inhibitor Associated Arthralgia: Effect of a Switch of AI

Methods

- 179 women ER+ EBC with severe musculoskeletal symptoms on anastrazole planning to stop treatment
- After 1/12 washout Rx 6/12 letrozole

Results

- 71% tolerated ongoing letrozole
- Fewer women had joint AEs after the switch

Switching from one AI to another (next step Tamoxifen) may improve arthalgia

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Briot et al.,

Systematic Review of Management Strategies for Aromatase Inhibitor Induced Arthalgia

- 21 studies, 12 interventions: major methodological limitations

Vitamin D

- Trials in favour but high risk of bias; 1 RCT- improvement in pain not function

Yoga / Exercise

- Studies in favour but small, inadequate controls; instructor style may influence outcomes

Acupuncture

- Mix positive/ negative outcomes across trials; Issues with sham acupuncture as placebo

Duloxetine

- Efficacy in uncontrolled trial, n=29

Nahm et al., 2018

Conclusions

- Menopausal symptoms are common after treatment for breast cancer
- Symptoms affect QOL to an extent that curative treatments can be discontinued prematurely
- Pharmacological / non-pharmacological approaches may improve patients symptoms
- A need remains for better access to support strategies as well as new interventions to manage these symptoms

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