SAMS South African Menopause Society

MENOPAUSE Matters

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Non-hormonal treatments for menopausal symptoms

The symptoms women experience through the menopause transition are physiologically attributed to estrogen deprivation. As ovarian function diminishes, the reduction of estrogen production effects all tissues that have estrogen receptors and one would be hard-pressed to find any exceptions.

The logical – and indeed the most effective treatment of menopausal symptoms – is menopausal hormone therapy, however for medical reasons and other concerns, some women prefer alternative methods of treating "vasomotor symptoms". These are primarily temperature instability manifesting as "hot flushes" and sleep disturbances.

Non-hormonal treatments – general

- **Lifestyle Modifications:** Attention to diet and exercise are keys to weight management which in turn may alleviate some menopausal symptoms. Smoking and alcohol intake should be early targets. Cognitive behavioural therapy can be effective in managing the psychological aspects of menopause and indirectly reduce the bothersome nature of hot flushes.
- **Herbal and Complementary Therapies:** Phytoestrogens found in soy and other plants can mimic estrogen in the body, though evidence of their effectiveness is mixed. Proof supporting herbal supplements' efficacy is inconsistent.

Non-hormonal treatments - medicinal

- **Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors:** Paroxetine is the most commonly used medication for this purpose. Others are venlafaxine and fluoxetine which can reduce hot flushes.
- **Gabapentin**: Originally used for epilepsy and neuropathic pain, gabapentin can help alleviate hot flushes, particularly at night.

- **Clonidine**: An alpha-2 adrenergic agonist traditionally used for hypertension, clonidine has been shown to provide some symptomatic relief, though it may cause side effects such as dry mouth and drowsiness.
- **Neurokinin receptor stabilisers**

Hypothalamic kisspeptin/neurokinin/dynorphin (KNDy) neurons play a role in thermoregulation. Declining estrogen levels during and after the menopause transition lead to hypertrophy and hyperactivity of KNDy neurons, with altered gene expression. This hyperactivation relates to disruption of thermoregulation, which may trigger symptoms. New medications belonging to a class of drugs known as neurokinin 3 receptor (NK3R) antagonists are now proven to be of value. By blocking specific receptors in the hypothalamus, these drugs regulate the temperature control centre, thus modulating vasomotor instability during the menopause.

Fezolinetant

Fezolinetant is a neurokinin 3 receptor antagonist, used for managing moderate-to-severe vasomotor symptoms. Its effectiveness in various doses, has been explored compared to placebo and the results published in the SKYLIGHT trials (Santoro et al *Menopause* 2024;32:247-57). The studies aimed to evaluate the change in vasomotor symptom frequency from baseline at week 12, considering several intrinsic (individual-related) and extrinsic (external influence) factors.

The results demonstrated that the active medication significantly reduced symptom frequency across all examined factors, with notable efficacy in participants over a wide spectrum of origins and habits. The treatment was generally well tolerated, showing comparable rates of treatment-emergent adverse events across all patient groups. The price of many hundreds of US$ per month remains a significant impediment to its wider use.

Elinzanetant

The OASIS clinical trials assessed the efficacy and safety of elinzanetant, a selective neurokinin-1,3 receptor antagonist, for treating moderate to severe vasomotor symptoms. The trials, conducted in the US, Europe, Canada, and Israel, included postmenopausal women who were experiencing moderate to severe vasomotor symptoms. Participants received either 120 mg of elinzanetant or a placebo for up to 26 weeks (Pinkerton et al *JAMA* 2024 doi 10.1001/jama.2024.14618).

The primary outcomes measured were the changes in the frequency and severity of symptoms from baseline to weeks 4 and 12. Elinzanetant significantly reduced both

the frequency and severity of symptoms compared to the placebo, with improvements observed as early as week 4 and sustained through week 12. Additionally, elinzanetant was associated with significant improvements in sleep disturbances and menopause-related quality of life.

The safety profile was favourable, with most participants completing the full trials. The results suggest that elinzanetant is a well-tolerated and effective nonhormonal treatment option for moderate to severe symptoms in postmenopausal individuals.

Renewed interest in menopause management?

Does the discovery of these "non-hormonal" medications change the dialogue on the management of the menopause?

The understanding of the actual mechanisms causing vasomotor symptoms clarifies the professions' position when new drugs are brought to market and allows a rational approach to treatment options. This must enhance the quality of therapeutic discussions which have been exclusively "estrogen-based" for almost a century.

Is this "A New Era in Menopause Management" as suggested in an editorial (Faubion et al *JAMA* 2024 doi 10.1001/jama.2024.15118). With acknowledgments to *JASS*.

Does transdermal nitroglycerin help?

A randomised, double-blind, placebo-controlled trial investigated the impact of continuous transdermal nitroglycerin (NTG) therapy on sleep quality in menopausal women with frequent hot flushes.

The study involved 140 peri- and postmenopausal women, who received either NTG or placebo patches for 12 weeks. Both groups saw a reduction in nocturnal hot flushes and sleep disruption, with no significant differences between the NTG and placebo groups. However, improved hot flush frequency was linked to better sleep quality and reduced sleep disruption.
The trial confirms that time or the placebo effect can reduce hot flush frequency can improve sleep in menopausal women. NTG did not show added benefits compared to placebo in sleep outcomes over the 12-week period (Pei et al *Am J Obs Gyn* 2024).

Menopausal hormone therapy and ageing

A study from the United Kingdom explores the relationship between menopausal hormone therapy (MHT), socioeconomic status, and biological aging in postmenopausal women. Using data from more than 100,000 postmenopausal women in the UK Biobank, the research examines how MHT impacts the discrepancy between chronological age and biological age, as measured by phenotypic age, which is a biomarker-based assessment of aging (Liu et al *JAMA Netw Open* 2024;7:e2430839).

The findings reveal that women who used MHT had a smaller biological aging discrepancy compared to those who never used MHT, indicating they were biologically younger relative to their chronological age. This effect was particularly pronounced in women with lower socio-economic status, suggesting that MHT might mitigate some of the aging-related disadvantages associated with lower socioeconomic positions. Women who started MHT at age 55 or older and those who used MHT for four to eight years exhibited the most significant reductions in biological aging discrepancy.

Additionally, the study found that the smaller aging discrepancy mediated the association between MHT use and decreased mortality risk, accounting for approximately 13% of the reduction in all-cause and cause-specific mortality, particularly cardiovascular disease mortality. This suggests that part of the mortality benefit associated with MHT may be due to its impact on biological aging.

The study emphasises the potential role of MHT in promoting healthy aging, particularly among socioeconomically disadvantaged women.

Weight loss drugs with and without MHT

The new semaglutide set of weight-loss medications are widely used, but their combination effect with menopausal hormone therapy is unknown. A study has been published of 106 women, 16 of whom were on MHT and 90 not on MHT. Results showed that women on MHT experienced significantly greater total body weight loss at 3, 6, 9, and 12 months compared to those not on MHT (Hurtado et al *Menopause* 2024;31:266-74).

At 12 months, MHT users achieved an average of 16% weight loss compared to 12% in non-MHT users, with more women on MHT reaching ≥5% and ≥10% weight reduction. Both groups saw improvements in cardiometabolic risk markers,

including glucose, blood pressure, and lipids. The association between MHT use and greater weight loss persisted after adjusting for confounding factors. The study suggests that MHT may enhance the weight loss effects of semaglutide in postmenopausal women.

Treatment of the Genitourinary Syndrome of Menopause

A study has investigated the short- and long-term efficacy of polycarbophil vaginal gel in treating the Genitourinary Syndrome of Menopause, or more specifically vaginal atrophy, in peri- and post-menopausal women. A total of more than 80 sexually active women were treated with PCV twice weekly for 30 days, and most opted to continue treatment for an additional 180 days (Cagnacci et al *EJOG & Rep Bio* 2024;299:303-8).

Baseline evaluations showed that post-menopausal women had more bothersome symptoms compared to peri-menopausal women. After 30 days, significant improvements were observed in both groups in the vaginal health index and in symptoms of vaginal dryness, irritation, pain, and global symptom scores, with post-menopausal women experiencing more pronounced benefits.
Prolonging treatment to 210 days led to further improvements across all measures, with no reported side effects.

The study demonstrated that PCV is an effective and safe treatment for local symptoms, and its efficacy increases with prolonged use. The authors concluded that PCV offers a valuable therapeutic option for addressing local symptoms, with potential for greater benefits over extended durations.

Supplements and Additives

A vast number of people take supplements in the form of vitamins, minerals and other additives. These do little if any good if the person is healthy and follows a balanced diet. The desire to be "doing something" to improve one's health seems deeply embedded in peoples' collective psyche.
Your editor is a cynic about their use, but this does not stop him reading the literature as follows:
Multivitamins: A study comprising nearly 400,000 healthy US adults investigated the association between long-term daily multivitamin use and mortality over more than 20 years.

The findings revealed no significant mortality benefit from multivitamin use. Despite nearly one-third of US adults taking multivitamins primarily for disease prevention,

this study suggests that such usage does not contribute to increased longevity (Loftfield et al *JAMA Netw Open* 2024;7:e2418729).

The research, incorporating data from three prospective cohorts, accounted for potential confounders, including healthy lifestyle and reverse causation. Ultimately the efficacy of multivitamin use in improving lifespan appears unsupported by these cohort findings.

Fish oil supplements: The use and benefits of omega-3/fish oil supplements are complex. It appears that "Regular use of fish oil supplements might be a risk factor for atrial fibrillation and stroke among the general population but could be beneficial for progression of cardiovascular disease from atrial fibrillation to major adverse cardiovascular events, and from atrial fibrillation to death." (Chen et al *BMJ Medicine* 2024;3:e000451).

Over the counter fish oils are not the same as prescription omega-3 medications. Neither should be substitutes for rarely or never eating fish which in America is recommended to be one to two servings per week (Manson *Medscape* 2024). Medical advice is recommended for commencing specialised supplements especially for those at risk of cardiovascular disease.

Aspirin: Many people take aspirin a primary prevention against colorectal cancer and many more have it prescribed as protection against secondary ischaemic cardiovascular events. However, it is unproven whether enteric-coated aspirin offers greater safety or reduces effectiveness compared to uncoated aspirin in patients with atherosclerotic cardiovascular disease.

In a trial that included more than 10,000 participants who were followed for two years, there were no significant differences between enteric-coated and uncoated aspirin in terms of effectiveness (measured by death, myocardial infarction, or stroke) or safety (measured by major bleeding events). The findings suggest that enteric-coated aspirin does not offer improved safety or effectiveness compared to uncoated aspirin, regardless of the dose, and patients can choose based on personal preference (Sleem et al *JAMA Cardiol* 2023;8:1061-9).

Endometrial polyps in the post-menopause

An investigation from the United States looked at the prevalence and risk factors for endometrial polyps in asymptomatic postmenopausal women with uterovaginal prolapse. Conducted as a cross-sectional analysis, it involved more than 300 women

who underwent hysterectomy for prolapse without a history of postmenopausal bleeding.

The researchers found that a third of these women had endometrial polyps, with an average polyp size of 13 mm and endometrial thickness of 1.4 mm. The majority (80%) had solitary polyps (Weigel et al *AJOG* 2024 doi 10.1016/j.ajog.2024.08.001).

Although premalignant or malignant lesions were rare (2%), the study identified two cases, including one of endometrial carcinoma. Risk factors for the presence of polyps included a higher body mass index and the use of menopausal hormone therapy. Specifically, the study noted that a higher BMI was associated with a 6% increased risk of polyps, and hormone therapy use was linked to a two thirds higher risk.

Despite the low malignant potential of these polyps, the study suggests that expectant management may be appropriate for incidentally found asymptomatic polyps.

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