SAMS South African Menopause Society

MENOPAUSE Matters

December 2024

MHT and dementia

The fact that women suffer from dementia more commonly than men is a source of ongoing exploration. This is not an issue of women versus men, but it is of interest why the difference exists so that the origins or predisposition to the condition can be researched and addressed therapeutically.

The search for early markers of cognitive impairment or early dementia is focussed on biochemical, biophysical or hormonal measures.

The biochemical indicators are related to general cardiovascular integrity since vascular and cerebral functions are intimately related, and the fact that lifestyle and cognition are so closely linked (Dhana et al. *JAMA Neurol*. 2024;81:233-9). Specific tests are accurate in identifying certain dementias – for example amyloid-beta and tau protein blood levels in Alzheimer Disease (Brooks. *Medscape*. 2024).

The biophysical indicators using MRI are becoming much more sophisticated while the machines and the image interpretations are developing with astonishing speed through medical-bioengineering and AI (Saleh et al. *Alz Res Ther*. 2023. doi:10.1186/s13195-022-01121-5). This paper found that MHT was "associated with improved delayed memory and larger entorhinal and amygdala volumes in *APOE4* carriers only" so X-linked and genetic possibilities are further research options.

There may be a connection between the severity of estrogen withdrawal responses and cognitive function. A study from Latin America examined the relationship between menopausal symptoms and cognitive impairment in postmenopausal women with a mean age of 56 years (Calle et al. *Menopause*. 2024. doi:10.1097/GME.0000000000002422).

Using data from more than 1,000 women, researchers assessed menopausal symptoms via the Menopause Rating Scale and cognitive function through a reputable Cognitive Assessment Scale. Findings showed that 15% of participants had mild cognitive impairment (MCI), with those experiencing more severe menopausal symptoms having significantly higher MCI rates (mean MRS score of 15 vs. 10 in those without MCI, $P < 0.001$). Severe menopausal symptoms were associated with a 75% higher risk of MCI.

However, factors like lower body mass index, sexual activity, physical exercise, hormone therapy use, and higher education correlated with reduced MCI risk. These findings emphasise the complex interaction between menopausal symptoms, lifestyle, and cognitive health, suggesting that treating severe menopausal symptoms and promoting a healthy lifestyle enhances cognitive function in postmenopausal women.

Those wishing to know the current state of MHT and dementia can access "*Hormone Therapy and Dementia: What Do We Know?*" (Yasgur. *Medscape*. 2024).

Snippets about dementia

Medications for dementia.

The holy grail of pharmaceutical companies is a drug that arrests or even reverses dementia. No such candidates have been trialled, with the closest those which claim to slow progression of the disorder.

The theory is that antibodies can clear cerebral amyloid, (which they can) but the clinical effect is weak, there are significant safety risks, and the drug costs are substantial – in the region of US$32,000 per annum. Donanemab has to be administered by infusion and fatalities have been reported (Manly et al. *JAMA*. 2023. doi:10.1001/jama.2023.11704 and Sims et al. *JAMA*. 2023. doi:10.1001/jama.2023.13239). For these reasons it has not been cleared by NICE for public distribution in the UK. Although a similar drug has been approved by the FDA in the US (Leqembi^{R}), it has disadvantages of the same nature (Leo et al. *Medscape*. 2023 and Sheinin. *Medscape*. 2023).

For a resume of these antibody treatments, see Heneka et al. *Lancet*. 2024.

Young onset dementia.

Although dementia incidence increases with age, its onset prior to 65 years old does occur and is called Young Onset Dementia. Its personal, societal and economic impact is particularly devastating and the associated risk factors spread across socio-economic, genetic and lifestyle domains (Hendriks et al. *JAMA Neurol*. 2024;81:134-42). It occurs most commonly around 55 years.

Dementia diagnostic blood test references are Vega. *Medscape*. 2024 and Palmqvist et al. *JAMA*. 2024; doi:10.1001/jama.2024.13855.

MHT & the vaginal microbiome

A study from China compared the vaginal microbiota patterns among premenopausal, postmenopausal and postmenopausal women using menopausal hormone therapy (MHT) (Lan et al. *Menopause*. 2024. doi:10.1097/GME.0000000000002432).

Among 94 participants, results revealed that postmenopausal women had a reduced Lactobacillus abundance (18%) and higher levels of anaerobic bacteria, along with greater microbial diversity, compared to premenopausal women. Postmenopausal women using MHT showed a higher Lactobacillus presence (54%) and lower microbial diversity, resembling the microbiota profile of premenopausal women.

Additionally, women with moderate to severe genitourinary syndrome of menopause (GSM) symptoms were linked to lower Lactobacillus levels and increased microbial diversity. These findings suggest that MHT may help restore a more Lactobacillus-dominant, lower-diversity

vaginal microbiome in postmenopausal women, potentially alleviating GSM symptoms. However, further research in larger cohorts is needed to confirm these preliminary observations and clarify MHT's role in maintaining vaginal microbiota balance.

Editorial comment. This research suggests that MHT maintains or restores a more pre-menopausal vaginal microbial environment than sham treatment and this is presumably why it is associated with fewer genito-urinary symptoms. This may appear self-evident to many of us, but this small study adds scientific under-pinning to symptom alleviation in GSM.

Post-op instructions after pelvic organ prolapse surgery

A randomised clinical trial examined whether expedited activity instructions are noninferior to standard restrictions after minimally invasive pelvic organ prolapse (POP) surgery. Conducted in a cohort of more than 100 women, the study evaluated anatomic and symptomatic outcomes at 3 months post-surgery (O'Shea et al. *JAMA Surg*. 2023; doi:10.1001/jamasurg.2023.1649).

Unnecessarily restricting postoperative activity may not be benign. The arbitrary limitation of patients' postoperative activity level could influence postoperative deconditioning, weight gain, and venous thromboembolism risk.

Results showed that patients who resumed physical activities without restrictions had comparable outcomes to those with prescribed limitations. Anatomic support and symptom severity were similar between both groups, which suggests that patients can safely resume activities ad lib after POP surgery without risking worse anatomical or symptomatic outcomes. The study supports revising traditional, non-evidence-based postoperative restrictions, allowing for a more liberal approach to activity post-surgery. These findings provide reassurance for both patients and providers that early return to activity does not adversely affect recovery after minimally invasive POP repair.

A heads-up on analgesia for seniors

Gabapentinoids have been marketed as a safer alternative to opioids for the treatment of neuropathic pain. In the form of pregabalin or gabapentin they are being increasingly prescribed in older patients for a variety of symptoms.

However, there are suggestions from an Australian study "that in addition to the known risk associated with kidney impairment, gabapentinoids should be used with caution among patients at risk of hip fractures, especially those who are frail." (Leung et al. *JAMA Netw Open*. 2024; doi:10.1001/jamanetworkopen.2024.44488)

Fezolinetant – further information

Fezolinetant, the neurokinin 3 receptor antagonist for bothersome menopausal symptoms, offers a promising non-hormonal option for women unable or unwilling to use hormonal therapy. Earlier research was from the Skylight trials (Santoro et al *Menopause* 2024;32:247-57)

The Daylight clinical trial evaluated fezolinetant in more than 400 women unsuitable for hormonal therapy, with results showing significant reductions in the frequency and severity of vasomotor symptoms compared to placebo, and improvements noted within one week. Adverse events were mostly mild, with a low discontinuation rate (5%), supporting fezolinetant's favourable safety profile (Schaudig et al. *BMJ.* 2024;387:e079525).

With data from 16 countries and more promised from Asian sources, fezolinetant represents a viable alternative for diverse populations, addressing an unmet need in menopausal care (Geraci et al. *BMJ* 2024;387:q2486).

Editor's comment: A "viable alternative" is an attractive expression, but it suggests that it is available and affordable. Both these conditions are questionable due to supply and retail costs. The price in the United States is about US$600 per month – that is $20 per tablet.

Vaginal Estrogen Use in Breast Cancer Survivors

A systematic review and meta-analysis assessed the safety of vaginal estrogen therapy (VET) in breast cancer survivors, focusing on recurrence, breast cancer-specific mortality, and overall mortality (Beste et al. *AJOG*. 2024).

The findings confirm that topical estrogen does not significantly increase the risk of breast cancer recurrence (OR, 0.48), breast cancer-specific mortality (OR, 0.60), or overall mortality (OR, 0.45). This review is in keeping with European conclusions (Cold et al. *JNCI.*2022;114:1347–54).

The analysis used robust statistical methods, including random-effects modelling and the Fragility Index, to ensure reliability. These results provide reassurance that VET can be safely used to manage genitourinary syndrome of menopause in breast cancer survivors without compromising oncologic outcomes.

Yet another publication supports the review's finding, this time from the analysis of 50,000 UK women with breast cancer. Clinical results were expressed as follows "there was no evidence of an increase in early breast cancer–specific mortality with use of vaginal estrogen therapy compared with no hormone replacement therapy use after breast cancer diagnosis." (McVicker et al. *JAMA Oncol*. 2024; doi:10.1001/jamaoncol.2023.4508).

Energy device decision

The latest Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) newsletter carries a report about energy devices, including equipment used in the treatment of the Genito-Urinary Syndrome of Menopause.

Following previous statements from *The US Food & Drug Administration* (2018) and RANZCOG (2022) the Australian Government undertook a post-market review of energy-based devices for the purpose of gynaecological treatments that use radiofrequency as well as carbon dioxide or other lasers. This was carried out by the Therapeutic Goods Administration a branch of the Department of Health and Aged Care. The review found:

- There was insufficient clinical evidence to support the therapeutic use and long-term safety of these devices.
- All energy-based devices intended to be used for vaginal rejuvenation sold in Australia have now had their registration as therapeutic products cancelled.
- They advise consumers and healthcare professionals that there are currently no devices included in the Australian Register of Therapeutic Goods approved for use for vaginal rejuvenation.

Athol Kent **Email address atholkent@mweb.co.za**