SAMS
South African Menopause Society

MENOPAUSE Matters

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Cognitive function

Cognitive function relates to our ability to think, feel, act, and interact with our environment.
It is intimately associated with our health in the following domains: physical, mental, emotional, social, and it is age related. The latter reveals itself with cognitive decline, which is inevitable, but the rate of decline, and particularly the experience of acute episodes of dysfunction, can be concerning and may be the covert reason for patients seeking a consultation.

This has been accentuated by the effects of Covid on the brain, both in the acute stages (How COVID-19 Affects the Brain – Boldrini et al *JAMA Psychiatry* 2021;75:682-3) and in the post-acute sequelae (Oh et al *JAMA Netw Open* 2021;4:e2119335). If your patient does self-report mental problems, even at extended time intervals post Covid infection (up to eight months) then an appropriate history and assessment is warranted (Soraas et al *JAMA Netw Open* 2021;4:e2118717 and Becker et al *JAMA Netw Open* 2021;4:e2130645).

Adding to any psychological or somatic pathology are spells of social isolation where the lack of human contact is a clear aggravating factor in accelerating cognitive decline – and it is measurable by brain imaging (Salinas et al *JAMA Netw Open* 2021;4:e2121122). This can be ameliorated by "supportive listening" so familial and friendship bonds can slow what is often seen as an inexorable process.

Any confusion, depression, anxiety, or memory loss should trigger questions about a Covid history.

Cognitive decline

Senescence is the process of deterioration with age, and there is a natural reduction of cognitive capacity and speed which is called cognitive decline. In previous issues of Menopause Matters the effects of an early reduction in endogenous hormones have been discussed in terms of oophorectomy or early menopause, causing accelerated cognitive dysfunction. The effect may be hormonal or be mediated through the development of atherosclerotic cardiovascular disease which can result in decreased tissue perfusion, and not necessarily major adverse cardiac or cerebral events (Freaney et al *JAMA Cardiol* 2021;6:1463-5). Cardiovascular disease is associated with cognitive decline in women more strongly than in men in longitudinal studies, so preventative and remedial factors can be crucially important (Huo et al *Neurology* 2022 doi 10.1212/WNL 0000000000013174).

While on the topic of cardiac health and mental health, there is a U-shaped association between blood pressure and dementia risk, as well as mortality, so routine blood pressure monitoring should be obligatory (Van Dalen et al *JAMA Int Med* 2021 doi 10.1001/jamainternmed.2021.7009).

The famous US Study of Women's Health Across the Nation (SWAN) showed that obesity, smoking, activity limitation, depressive symptoms, and CVD were linked to declines in physical and mental function – all of which are amenable to modification.

In addition, the following factors increase the rate of cognitive decline and/or the greater risk of dementia:

- Falls, fractures and immobilisation. The assessment of any older person should encompass fall-risk, which includes mobility and exercise programmes, osteoporosis management, medication revision, and an environmental review (Montero-Odasso et al *JAMA Netw Open* 2021;4:e2138911).

A fall in an elderly patient is so likely, that it should be anticipated. Fall trauma carries with it consequences that include cognitive decline so preventative measures should be part of any advice to a frail person, their family and care providers. There are practical guidelines that have been rigorously examined (Montero-Odasso et al *JAMA Netw Open* 2021;4:e2138911) and the effects measured (Szanton et al *JAMA Netw Open* 2021;4:e2122325).

These are sensible topics to cover in the general care of our older patients.

- Thyroid dysfunction. If there is no evidence of overt thyroid disease, there is no reason to embark on thyroid screening, as subclinical hyper- or hypo-thyroid abnormalities are not associated with cognitive decline (Van Vliet et al *JAMA Intern Med* 2021 doi 10.1001/jamainternmed.2021.5078).
- Vision. Loss of visual acuity can increase frailty and increase the risk of loss of mental function, especially if cataracts are present. A study comparing cataract extraction with no surgery demonstrated a significantly reduced risk of dementia and should be specifically investigated (Lee et al *JAMA Int Med* 2021 doi 10.1001/jamainternmed.2021.6990).
- Hearing. Loss of hearing is common at speech frequency and, if uncorrected, leads to accelerated cognitive disability (Yevenes-Briones et al *JAMA Otolaryngol Head Neck Surg* 2021 doi 10.1001/jamaoto.2021.2399).
- Coffee. It is difficult to prove associations of food and drink intake with health outcomes, unless extensive longitudinal data are available. An Australian study over a decade showed that increased coffee drinking had a positive relationship with decreased cognitive decline and less Aβ-amyloid accumulation in the brain (Gardener et al *Aging Neurosci* 2021 doi 10.3389/fnagi.2021.744872). The researchers speculate that greater coffee consumption may be protective against the development of Alzheimer's Disease.
- Sleep. The duration of sleep is also linked to rates of cognitive decline, with 6 to 8 hours being the "official normal" range (Ma et al *JAMA Netw*

Open 2020;3:e2013573).

- Hospitalisation. Even short stays in hospital can negatively affect older people – their physical and mental faculties taking a prolonged time to recover – but exercise programmes, while an inpatient, can ameliorate deterioration (Martinez-Velilla et al *JAMA Int Med* 2021 doi 10.1001/jamainternmed.2021.7654).
- Cancer-related cognitive effects. Cognitive impairment related to malignancy, especially breast cancer, was originally thought to be due to chemotherapy, but this now seems unlikely. Systemic inflammatory processes are more probably candidates in explaining cognitive decline with the diagnosis and treatment of cancers (Van Dyk et al *JAMA* 2021;326:1736-7).

Mood disorders

Mood swings or symptoms of depression and anxiety disorders are common as women age. The range of interventions is wide, from formal therapies to supplements but the effectiveness of these modalities vary considerably.

The most effective form of treatment is cognitive behavioural therapy (CBT), but group and individual yoga; although not as effective; can reduce general anxiety symptoms (Simon et al *JAMA Psychiatry* 2021;78:13-20).

Depression can be precipitated by a myriad of influences but an easily overlooked source may be visual impairment. Poor eyesight is surprisingly common and unrecognised so it may be a simple and rewarding avenue to pursue from midlife on (Karvonen-Gutierrez et al *Menopause* 2022:29:35-41).

Supplements are of no value in healthy people. They have no place in any serious medical discussion but this does not prevent the public from swallowing vitamins and minerals of increasing quantities, colours, fizziness and falling for advertising gimmicks. To be clear the following articles make the point:

- Omega 3 fatty acids (PUFAs) do not prevent depression as shown in a randomised trial of more than 18 000 participants (Okereke et al *JAMA*

2021;326:2385-94)
- PUFAs do not help high-risk CVD people – even at high levels (Slomski *JAMA* 2021;326:19)
- Supplements do not protect against cancer or CVD (Nelson USPSTF 2014 & updated 2021)

Editor's comment – I am emotionally opposed to supplements as I do not believe they work, but to be intellectually honest I have to keep an open mind. I do read articles that describe research, positive and negative and came across one this month that claims success (Liu et al JAMA Netw Open 2022;5:e2144279). It is a small trial (33 subjects in each arm) comparing urolithin A with placebo for improved muscle performance in people with a mean age of 72 years. The results of the secondary endpoints of muscle endurance and biomarkers were in favour of the active substance and the researchers state urolithin A "is a promising approach to counteracting age-associated muscle decline." We shall see if subsequent work supports this result.

Osteoporosis checked out

- Osteoporosis is characterised by both decreased bone mineral density (BMD) and deleterious changes to bone microarchitecture.
- Any fracture in a person over the age of 50 years increases the risk of a repeat fracture, regardless of BMD, and there is no advantage in classifying a fracture as traumatic or atraumatic.
- Indications for antiresorptive therapy include any fracture or a dual-energy x-ray absorptiometry T score of – 2.5 or lower.
- First-line treatment is with bisphosphonates for example: alendronate – 70mg per week (US$85 per month) or risedronate 35mg weekly or 150mg monthly (US$650 per month).

Treatment should be continued for five years and the situation reassessed with a validated fracture assessment tool. If low risk, cease treatment and reassess in

two years. If high risk, continue treatment or consider another class of medication (Silverstein et al *JAMA Intern Med* 2021;181:1635-6).

Bisphosphonate "**time to benefit**" is an important factor in considering initiation of therapy. This is the duration of treatment required to avoid one non-vertebral fracture per 100 high-risk patients. This time-frame is one year for commonly used bisphosphonates (Deardorff et al *JAMA Intern Med* 2021 doi 10.1001/jamainternmed.2021.6745). Put plainly, 100 patients taking bisphosphonates for one year will not eliminate all fractures but will reduce the number of fractures by one.

As an additional fact, dermatologists assure us that protecting one's skin does not increase the risk of osteoporosis. Avoiding direct sunlight, wearing long sleeves, and using sunscreen lotions does not reduce vitamin D accumulation to the detriment of bone health (Afarideh et al *JAMA Dermatol* 2021;157:1437-46).

Of course prevention is the best option and exercise offers much to maintain bone integrity, but what type of activities are recommended to reduce fracture risks? It seems that "high-intensity resistance and impact training (HiRIT)" is more effective low-intensity programmes according to a study conducted in vulnerable women (Kistler-Fischbacher et al *JBMR* 2021 doi 10.1002/jbmr.4334). In a head-to-head comparison between HiRIT and Pilates schedules, the more rigorous regimen proved better in terms of gains in bone mineral density but both improved functional performance.

The point is to get sedentary women into active programmes and the empirical evidence provided by this study gives scientific impetus to what is advised.

Endometriosis and early menopause

Endometriosis is the presence of endometrial stroma outside the uterus. It is a chronic inflammatory condition which sometimes is associated with peritoneal

fluid "that contains more activated proinflammatory, chemotactic, and oxidative stress factors." Other features can include ovarian endometriomas that may cause infertility and decreased ovarian reserve.

The onset of the menopause transition is determined by the number of oocytes at birth, the rate of atresia, and ultimately ovarian ability to produce hormones cyclically. All these factors are in play with endometriosis and previous studies have linked it with early menopause, defined as the transition before the age of 45 years. Now the **Nurses' Health Study II** comprising more than 100,000 women with comprehensive follow-up, has shown that those with laparoscopically proven endometriosis are at higher risk of an early menopause (Kulkarni et al *JAMA Netw Open* 2022;5:e2144391). This was especially likely if the woman was nulliparous and never used oral contraceptives.

Ovarian cancer surgery

There are two reported advances in the surgical management of ovarian cancer.

Firstly, patients who have had an initially good response to surgery and platinum chemotherapy for ovarian cancer can suffer a relapse and this poses a therapeutic dilemma. Should they receive further courses of chemo with or without a second round of cyto-reductive surgery?

The results of a randomised trial suggest that surgery plus chemo provides extended survival compared with chemo alone. The survival time in those being operated on prior to chemo was 54 months, and in the chemo alone group, it was 46 months. Those in the surgical group in whom complete resection was possible (about three quarters) had a survival time of 60 months. There was no difference in quality-of-life measures between the groups (Harter et al *NEJM* 2021; 385:2123-31).

Commenting on the trial, an editorial reiterates the importance of experienced surgeons being involved in such operations because of the complexity of

potential accompanying procedures and it was noted that the mean operating time was nearly 4 hours. The editors also comment that poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors have an increasing role to play in the overall management of the disease (Gardner & Chi *NEJM* 2021; 385:2187-8).

Secondly, an additional aid has been developed to assist in identifying malignant tissue during surgery.
Pafolacianine is an optical imaging agent that is given intravenously pre-operatively to help the surgeon define lesions that may be missed by routine visual and palpation techniques.

Folate receptors are over-expressed in ovarian cancer cells and pafolacianine binds to these receptors and fluoresces under infrared light. In a research programme this adjunct allowed a quarter more malignant lesions to be detected thus aiding the debulking process (Voelker *JAMA* 2022;327:27) and FDA approval has been granted for its use.

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Menopause Matters is a monthly review of matters menopausal that have recently appeared in the journals. It is produced for the South African Menopause Society and the summaries concentrate on clinical issues although some underlying patho-physiology will be included to ensure a scientific basis for the work. These summaries and opinions do not necessarily reflect the views of the S A Menopause Society. Any clinical decisions made on the data presented are at the reader's discretion.