Letters to the Editor

Evidence-based management of menopause

Magraith and Jang's menopause review[1] contains unsupported claims. Menopausal hormone therapy (MHT) is characterised as 'highly effective' and 'the most effective treatment' for menopausal symptoms. A list of symptoms includes sleep disturbance, mood changes, cognitive concerns and musculoskeletal symptoms, which are not actually menopausal. Neither the purported benefits nor harms of MHT are quantified, except for a doubling or tripling of venous thromboembolism (VTE) risk. However, absolute risk of VTE is described only as remaining low. Risks of heart attack, stroke and breast cancer, similarly, remain unquantified.

The claim that menopause – rather than ageing per se – is associated with increased risk of cardiovascular disease is supported not by research evidence, but by an International Menopause Society guideline.[2] Among the guideline's 21 authors, 14 report pharmaceutical industry funding. A claim that good evidence supports MHT's role in preventing cardiovascular disease cites a Cochrane review; however, this review concludes there is 'strong evidence that treatment with hormone therapy in post-menopausal women overall, for either primary or secondary prevention of cardiovascular disease events has little if any benefit…'.[3]

A claim that there is no maximal duration of MHT use is similarly cavalier; based on the UK Million Women study, 5 years use of estrogen plus progestogen leads to 6 extra breast cancers per 1000 users; 10 years use leads to 19 extra breast cancers per 1000 users.[4]

Readers of *Australian Prescriber* deserve evidence-based recommendations.

Barbara Mintzes
Professor, School of Pharmacy and Charles Perkins Centre, Faculty of Medicine and Health, The University of Sydney
General Secretary, International Society of Drug Bulletins
Associate Editor, *Drug and Therapeutics Bulletin*

Conflicts of interest: none declared

REFERENCES

1. Magraith K, Jang C. Management of menopause. Aust Prescr 2023;46:48-53. https://doi.org/10.18773/austprescr.2023.014
2. Baber RJ, Panay N, Fenton A, Group IMSW. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric 2016;19:109-50. https://doi.org/10.3109/13697137.2015.1129166
3. Boardman HM, Hartley L, Eisinga A, Main C, Roque i Figuls M, Bonfill Cosp X, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst Rev 2015;2015:CD002229. https://doi.org/10.1002/14651858.CD002229.pub4
4. Beral V, Million Women Study C. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419-27. https://doi.org/10.1016/s0140-6736(03)14065-2

McGraith and Jang's article on menopause makes statements and draws conclusions that are not supported by evidence.[1] Pharmaceutical companies have attempted to attribute all symptoms associated with ageing to menopause,[2] but the only symptoms proven to be associated with menopause are hot flushes and vaginal dryness.[3] The authors describe quality of life as an established benefit of MHT, but there is no evidence that MHT improves quality of life unless a woman is having severe hot flushes.[4]

The authors also imply that MHT prevents cardiovascular disease when neither estrogen alone nor estrogen plus progestogen combinations demonstrated this benefit in the Women's Health Initiative (WHI) trial or in any other randomised controlled trial.[5,6]

The consequences of serious adverse effects are underestimated in this article. Estrogen plus progestogen combinations increase the risk of stroke, double the risk of VTE and dementia, and increase the risk of incontinence.[7] Estrogen alone increases the risk of stroke.[6] When the WHI study identified that the harms of MHT outweighed its benefits,[5,6] the corresponding drop in prescribing MHT was associated with a decrease in breast cancer rates around the globe, including in Australia.[8]

Adriane Fugh-Berman
Professor and Physician, Georgetown University Medical Center, Washington DC

Conflicts of interest: Adriane Fugh-Berman is a paid expert witness in litigation regarding pharmaceutical marketing, and has previously been a paid expert witness in litigation regarding the promotion of menopausal hormone therapy.

REFERENCES

1. Magraith K, Jang C. Management of menopause. Aust Prescr 2023;46:48-53. https://doi.org/10.18773/austprescr.2023.014

Keywords
cardiovascular disease risk, estrogen, menopausal hormone therapy, progestogen, venous thromboembolism

Aust Prescr 2024;47:43–5
https://doi.org/10.18773/austprescr.2024.017

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

LETTERS

2. Fugh-Berman A. The Science of Marketing: How Pharmaceutical Companies Manipulated Medical Discourse on Menopause. Women's Reproductive Health 2015;2:18-23. https://doi.org/10.1080/23293691.2015.1039448
3. National Institutes of Health. NIH State-of-the-Science Conference Statement on management of menopause-related symptoms. NIH Consens State Sci Statements 2005;22:1-38. https://pubmed.ncbi.nlm.nih.gov/17308548/
4. Utian WH, Woods NF. Impact of hormone therapy on quality of life after menopause. Menopause 2013;20:1098-105. https://doi.org/10.1097/GME.0b013e318298debe
5. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33. https://doi.org/10.1001/jama.288.3.321
6. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701-12. https://doi.org/10.1001/jama.291.14.1701
7. Fugh-Berman A, Scialli AR. Gynecologists and estrogen: an affair of the heart. Perspect Biol Med 2006;49:115-30. https://doi.org/10.1353/pbm.2006.0006
8. Kumle M. Declining breast cancer incidence and decreased HRT use. Lancet 2008;372:608-10. https://doi.org/10.1016/S0140-6736(08)61255-6

Karen Magraith and Christina Jang, the authors of the article, comment:

We thank Fugh-Berman and Mintzes for their Letters to the Editor regarding our article and we appreciate the opportunity to respond.

The symptoms associated with menopause are well recognised. While hot flushes and genitourinary symptoms are the most frequently encountered, a multitude of studies describe women reporting a range of other symptoms associated with menopause.[1-4]

We disagree that we have understated the risks associated with MHT. The baseline risk for VTE is 1 to 2 events in 1000 person-years;[5] for women taking MHT, the risk is 2 to 3 events in 1000 person-years, which is considered low.[6] Fugh-Berman states that estrogen plus progestogen combinations increased the risk of VTE, but fails to discuss that this is associated with the route of administration of estrogen and the type of progestogen used. Our article states that there is a thromboembolic risk associated with oral estrogen and that transdermal estrogen is preferred for women at risk. We note the author has referenced her own work from 2006,[7] which largely discusses the findings from the Heart and Estrogen/progestin Replacement Study (HERS)[8] and the WHI trial;[9,10] in both studies oral estrogen was the main therapy used. Since then, several observational studies have been published that found no association between transdermal estrogen and increased VTE risk.[11,12]

Fugh-Berman focuses on the risk of breast cancer associated with estrogen plus progestogen, referencing the WHI trial.[9,10] The combination of conjugated equine estrogens and medroxyprogesterone was the most commonly used regimen in this study, and the risk was only seen in women taking combination treatment, implicating the role of progestogens.[9,10] Our article has referenced a study that described a lower risk associated with micronised progesterone and dydrogesterone.[13] Until breast cancer rates have been studied for women using more modern forms of MHT, we would argue against attributing an increased risk of breast cancer to all forms of MHT equally.

Mintzes questions our referencing of the Boardman Cochrane review[14] and the evidence for MHT in cardiovascular disease prevention. We were referring to the subgroup analysis in the Cochrane review that focused on women starting MHT within 10 years after menopause and showed lower mortality and coronary heart disease in this group.[14] We have stated that MHT is not indicated for primary prevention of cardiovascular disease.

Our comment that there is no arbitrary limit for the use of MHT is consistent with major societal guidelines, including from the North American Menopause Society,[15] and a joint statement from the International Menopause Society, British Menopause Society, European Menopause and Andropause Society, Royal College of Obstetricians and Gynaecologists, and Australasian Menopause Society.[16]

The menopause experience is different for every woman. We have not recommended that all postmenopausal women use MHT; MHT can be offered to symptomatic women with no contraindications after a discussion about risk of harms versus benefits. We have presented evidence-based information and referenced studies published in peer reviewed journals. It is essential that women be given a balanced view of MHT, including up-to-date research, so that they can make an informed decision about their health.

REFERENCES

1. Maki PM, Jaff NG. Brain fog in menopause: a health-care professional's guide for decision-making and counseling on cognition. Climacteric 2022;25:570-8. https://doi.org/10.1080/13697137.2022.2122792
2. Freeman EW, Sammel MD, Lin H, Gracia CR, Pien GW, Nelson DB, et al. Symptoms associated with menopausal transition and reproductive hormones in midlife women. Obstet Gynecol 2007;110:230-40. https://doi.org/10.1097/01.AOG.0000270153.59102.40
3. Gracia CR, Freeman EW. Onset of the Menopause Transition: The Earliest Signs and Symptoms. Obstet Gynecol Clin North Am 2018;45:585-97. https://doi.org/10.1016/j.ogc.2018.07.002

4. Talaulikar V. Menopause transition: Physiology and symptoms. Best Pract Res Clin Obstet Gynaecol 2022;81:3-7. https://doi.org/10.1016/j.bpobgyn.2022.03.003
5. Lutsey PL, Zakai NA. Epidemiology and prevention of venous thromboembolism. Nat Rev Cardiol 2023;20:248-62. https://doi.org/10.1038/s41569-022-00787-6
6. Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ 2008;336:1227-31. https://doi.org/10.1136/bmj.39555.441944.BE
7. Fugh-Berman A, Scialli AR. Gynecologists and estrogen: an affair of the heart. Perspect Biol Med 2006;49:115-30. https://doi.org/10.1353/pbm.2006.0006
8. Grady D, Applegate W, Bush T, Furberg C, Riggs B, Hulley SB. Heart and Estrogen/progestin Replacement Study (HERS): design, methods, and baseline characteristics. Control Clin Trials 1998;19:314-35. https://doi.org/10.1016/s0197-2456(98)00010-5
9. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33. https://doi.org/10.1001/jama.288.3.321
10. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701-12. https://doi.org/10.1001/jama.291.14.1701
11. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ 2019;364:k4810. https://doi.org/10.1136/bmj.k4810
12. Rovinski D, Ramos RB, Fighera TM, Casanova GK, Spritzer PM. Risk of venous thromboembolism events in postmenopausal women using oral versus non-oral hormone therapy: A systematic review and meta-analysis. Thromb Res 2018;168:83-95. https://doi.org/10.1016/j.thromres.2018.06.014
13. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat 2008;107:103-11. https://doi.org/10.1007/s10549-007-9523-x
14. Boardman HM, Hartley L, Eisinga A, Main C, Roque i Figuls M, Bonfill Cosp X, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst Rev 2015;2015:CD002229. https://doi.org/10.1002/14651858.CD002229.pub4
15. "The Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause 2022;29:767-94. https://doi.org/10.1097/GME.0000000000002028
16. Hamoda H, Davis SR, Cano A, Morris E, Davison S, Panay N, et al. BMS, IMS, EMAS, RCOG and AMS joint statement on menopausal hormone therapy and breast cancer risk in response to EMA Pharmacovigilance Risk Assessment Committee recommendations in May 2020. Post Reprod Health 2021;27:49-55. https://doi.org/10.1177/2053369120983154