

Revised Global Consensus Statement on Menopausal Hormone Therapy

T. J. de Villiers^a, J. E. Hall^b, J. V. Pinkerton^c, S. Cerdas Pérez^d, M. Rees^e, C. Yang^f and D. D. Pierroz^g

^aMediClinic Panorama and Department of Gynecology, University of Stellenbosch, Cape Town, South Africa; ^bNational Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina, USA; ^cDepartment of Obstetrics and Gynecology, The University of Virginia Health System, Charlottesville, VA, USA; ^dEndocrinology Department, Hospital Cima, San José, Costa Rica; ^eReader Emeritus, University of Oxford, UK; ^fMount Alvernia Hospital, Singapore; ^gUniversity of Geneva, Switzerland

The following Consensus Statement is endorsed by The International Menopause Society, The North American Menopause Society, The Endocrine Society, The European Menopause and Andropause Society, The Asia Pacific Menopause Federation, The International Osteoporosis Foundation and The Federation of Latin American Menopause Societies.

Introduction

The publication of the Global Consensus on Menopausal Hormone Therapy in 2013 by leading global menopause societies succeeded in presenting guidelines in a troubled therapeutic area that are helpful to both health-care providers and potential users of menopausal hormone therapy (MHT). The revised statement is aimed at updating and expanding the areas of consensus. The revised statement is presented in bullet-point format to facilitate ease of use. The revised statement contains only areas of consensus and does not replace the more detailed and fully referenced recommendations of the individual societies (referenced at the end of the document). Hopefully, this statement will enable health-care providers to offer those women in midlife, who may benefit from MHT, the opportunity to make an informed decision.

Section A: Benefit/risk profile of MHT

- MHT, including tibolone and the combination of conjugated equine estrogens and bazedoxifene (CE/BZA), is the most effective treatment for vasomotor symptoms (VMS) associated with menopause at any age, but benefits are more likely to outweigh risks if initiated for symptomatic women before the age of 60 years or within 10 years after menopause.
- If MHT is contraindicated or not desired for treatment of VMS, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors such as paroxetine, escitalopram, venlafaxine and desvenlafaxine, which have been shown to be effective in randomized controlled trials (RCTs), may be considered. Gabapentin may also be considered.
- Quality of life, sexual function and other menopause-related complaints, such as joint and muscle pains, mood changes and sleep disturbances, may improve during MHT.

- MHT, including tibolone and CE/BZA, is effective in the prevention of bone loss in postmenopausal women.
- MHT has been shown to significantly lower the risk of hip, vertebral and other osteoporosis-related fractures in postmenopausal women.
- MHT is the only therapy available with RCT-proven efficacy of fracture reduction in a group of postmenopausal women not selected for being at risk of fracture and with mean *T*-scores in the normal to osteopenic range.
- MHT, including tibolone, can be initiated in postmenopausal women at risk of fracture or osteoporosis before the age of 60 years or within 10 years after menopause.
- Initiation of MHT after the age of 60 years for the indication of fracture prevention is considered second-line therapy and requires individually calculated benefit/risk, compared to other approved drugs. If MHT is elected, the lowest effective dose should be used.
- MHT, including tibolone, is effective in the treatment of vulvovaginal atrophy (VVA), now also considered as a component of the genitourinary syndrome of menopause (GSM). Local low-dose estrogen therapy is preferred for women whose symptoms are limited to vaginal dryness or associated discomfort with intercourse or for the prevention of recurrent urinary tract infections. Ospemifene, an oral selective estrogen receptor modulator, is also licensed in some countries for the treatment of dyspareunia attributed to VVA.
- RCTs and observational data as well as meta-analyses provide evidence that standard-dose estrogen-alone MHT may decrease the risk of myocardial infarction and all-cause mortality when initiated in women younger than 60 years of age and/or within 10 years of menopause.
- Data on estrogen plus progestogen MHT initiated in women younger than age 60 years or within 10 years of menopause show a less compelling trend for mortality benefit, and evidence on cardioprotection is less robust

CONTACT Dr T. J. de Villiers  tobie@iafrica.com  MediClinic Panorama, Parow 7500, South Africa

This Statement is being simultaneously published in the journals *Climacteric* and *Maturitas*, on behalf of the International Menopause Society and The European Menopause and Andropause Society, respectively.

with inconsistent results compared to the estrogen-alone group.

- The risk of venous thromboembolism (VTE) and ischemic stroke increases with oral MHT, although the absolute risk of stroke with initiation of MHT before age 60 years is rare. Observational studies and a meta-analysis point to a probable lower risk of VTE and possibly stroke with transdermal therapy (0.05 mg twice weekly or lower) compared to oral therapy.
- The risk of breast cancer in women over 50 years of age associated with MHT is a complex issue with decreased risk reported from RCTs for estrogen alone (CE in the Women's Health Initiative (WHI)) in women with hysterectomy and a possible increased risk when combined with a progestin (medroxyprogesterone acetate in the WHI) in women without hysterectomy. The increased risk of breast cancer thus seems to be primarily, but not exclusively, associated with the use of a progestin with estrogen therapy in women without hysterectomy and may be related to the duration of use.
- The risk of breast cancer attributable to MHT is rare. It equates to an incidence of <1.0 per 1000 women per year of use. This is similar or lower than the increased risk associated with common factors such as sedentary lifestyle, obesity and alcohol consumption. The risk may decrease after treatment is stopped, but data are inconsistent.
- Women experiencing a spontaneous or iatrogenic menopause before the age of 45 years and particularly before 40 years are at a higher risk for cardiovascular disease and osteoporosis and may be at increased risk of affective disorders and dementia. In such women, MHT reduces symptoms and preserves bone density. Observational studies that suggest MHT is associated with reduced risk of heart disease, longer lifespan, and reduced risk of dementia require confirmation in RCTs. MHT is advised at least until the average age of menopause.
- MHT initiated in early menopause has no substantial effect on cognition, but, based on observational studies, it may prevent Alzheimer's disease in later life. In RCTs, oral MHT initiated in women aged 65 or older also has no substantial effect on cognition and increases the risk of dementia.
- MHT may be beneficial in improving mood in early postmenopausal women with depressive and/or anxiety symptoms. MHT may also be beneficial for perimenopausal women with major depression but antidepressant therapy remains first-line treatment in this setting.

Section B: General principles governing the use of MHT

- The option of MHT is an individual decision in terms of quality of life and health priorities as well as personal risk factors such as age, time since menopause and the risk of VTE, stroke, ischemic heart disease and breast cancer. MHT should not be recommended without a clear indication for its use.
- Consideration of MHT for symptom relief or osteoporosis prevention should be a part of an overall strategy

including lifestyle recommendations regarding diet, exercise, smoking cessation and safe levels of alcohol consumption for maintaining the health and quality of life of peri- and postmenopausal women.

- MHT includes a wide range of hormonal products and routes of administration, including tibolone (where available) or CE/BZA, with potentially different risks and benefits. However, evidence regarding differences in risks and benefits between different products is limited.
- The type and route of administration of MHT should be consistent with treatment goals, patient preference and safety issues and should be individualized. The dosage should be titrated to the lowest appropriate and most effective dose.
- Duration of treatment should be consistent with the treatment goals of the individual, and the benefit/risk profile needs to be individually reassessed annually. This is important in view of new data indicating longer duration of VMS in some women.
- Estrogen as a single systemic agent is appropriate in women after hysterectomy but concomitant progestogen is required in the presence of a uterus for endometrial protection with the exception that CE can be combined with BZA for uterine protection.
- The use of continuous testosterone therapy, either alone or with MHT, is supported in carefully selected postmenopausal women with sexual interest/arousal disorder (in countries with regulatory approval).
- The use of custom-compounded hormone therapy is not recommended because of lack of regulation, rigorous safety and efficacy testing, batch standardization, and purity measures.
- Current safety data do not support the use of systemic MHT in breast cancer survivors, although discussions, in selected women and in conjunction with each woman's oncologist, may occur for compelling reasons after non-hormonal or complementary options have been unsuccessful.

Authors/members of the Consensus Panel

The International Menopause Society: Tobie J. de Villiers, *Past President*, Mediclinic Panorama and Department of Gynecology, University of Stellenbosch, Cape Town, South Africa; Rodney J. Baber, *President*, The University of Sydney, Sydney, Australia; Victor W. Henderson, *General Secretary*, Departments of Health Research & Policy (Epidemiology) and of Neurology & Neurological Sciences, Stanford University, Stanford, CA, USA; Nick Panay, *Co-Editor-in-Chief, Climacteric*, Imperial College London, UK; Anna Fenton, *Co-Editor-in-Chief, Climacteric*, Christchurch Women's Hospital, Christchurch, New Zealand; Mary Ann Lumsden, *Treasurer and President-Elect*, Department of Gynaecology and Medical Education (Reproductive and Maternal Medicine), Glasgow University, Glasgow, Scotland; Susan R. Davis, *Board Member*, Department of Endocrinology, Monash University, Melbourne, Australia; Steven R. Goldstein, *Treasurer-Elect*, Department of Obstetrics

and Gynecology at New York University School of Medicine, New York, USA.

The Endocrine Society: Janet E. Hall, *Past President*, National Institute of Environmental Health Sciences; Richard J. Santen, *Past President*, University of Virginia Health System; Cynthia A. Stuenkel, University of California, San Diego, School of Medicine.

The North American Menopause Society: JoAnn V. Pinkerton, *Executive Director*, Department of Obstetrics and Gynecology, The University of Virginia Health System, Charlottesville, VA, USA; Peter F. Schnatz, *President*, Department of Obstetrics and Gynecology, The Reading Hospital, Reading, PA, USA; Marla Shapiro, *President-Elect*, Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada; Pauline M. Maki, *Immediate Past President*, Departments of Psychiatry and Psychology, University of Illinois at Chicago, Chicago, IL, USA; James H. Liu, *Treasurer*, Department of Reproductive Biology, Case Western Reserve University School of Medicine, Cleveland, OH, USA; Gloria Richard-Davis, *Secretary*, Department of Obstetrics and Gynecology, University of Arkansas Medical Sciences, Little Rock, AR, USA; Wulf H. Utian, *Executive Director Emeritus*, Case Western Reserve University School of Medicine, Cleveland, OH, USA; **Board Members:** Lisa Astalos Chism, Women's Wellness Clinic, Karmanos Cancer Institute, Detroit, MI, USA; Howard N. Hodis, Division of Cardiovascular Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; Andrew M. Kaunitz, Department of Obstetrics and Gynecology, University of Florida College of Medicine, Jacksonville, Jacksonville, FL, USA; Sheryl A. Kingsberg, Departments of Reproductive Biology and Psychiatry, Case Western Reserve University School of Medicine, Cleveland, OH, USA; Katherine M. Newton, Group Health Research Institute, Seattle, WA, USA; Nanette F. Santoro, Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora, CO, USA; Lynnette Leidy Sievert,

Department of Anthropology, University of Massachusetts, Amherst, Amherst, MA, USA; Isaac Schiff, Department of Gynecology, Harvard Medical School, Boston, MA, USA.

European Menopause and Andropause Society: Margaret Rees, *Executive Director*, Reader Emeritus, University of Oxford, UK; Irene Lambrinoudaki, *President*, Department of Gynecological Endocrinology, University of Athens, Greece.

The Asia Pacific Menopause Federation: Chua Yang, *President*, A Clinic For Women, Mount Alvernia Hospital, Singapore.

The Federation of Latin American Menopause Societies: Sonia Cerdas Pérez, *President*, Endocrinology Department, Hospital Cima, San José, Costa Rica.

International Osteoporosis Foundation: Dominique D. Pierroz, *Science Manager*, Geneva University Hospital & Faculty of Medicine, Geneva, Switzerland.

Source of funding Nil.

Core references

- Baber RJ, Panay N, Fenton A, and the IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. *Climacteric* 2015;19:109–50
- Shifren JL, Gass ML; NAMS Recommendations for Clinical Care of Midlife Women Working Group. The North American Menopause Society recommendations for clinical care of midlife women. *Menopause* 2014;21:1038–62
- Stuenkel CA, Davis SR, Gompel A, *et al.* Treatment of symptoms of the menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2015;100:3975–4011
- Neves-e-Castro M, Birkhäuser M, Samsioe G, *et al.* EMAS position statement: The ten point guide to the integral management of menopausal health. *Maturitas* 2015;81:88–92
- de Villiers TJ, Gass ML, Haines CJ, *et al.* Global consensus statement on menopausal hormone therapy. *Climacteric* 2013;16:203–4
- Wierman M, Arlt W, Basson R, *et al.* Androgen therapy (testosterone and DHEA) in women: a reappraisal: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2014;99:3489–510