REVIEW OPEN ACCESS

Expert Opinion on Age-Related Sex Hormone Changes and Hypogonadism in People With Multiple Sclerosis

A Delphi Consensus Program

Riley Bove,[1] Manuela Simoni,[2] Camil Castelo-Branco,[3] Jorge Correale,[4,5] Kerstin Hellwig,[6] Maria K. Houtchens,[7,8] Melinda Magyari,[9,10] Gabriele Merki-Feld,[11] Scott Montgomery,[12,13,14] Rossella E. Nappi,[15,16] Wen Shen,[17] Egon Stenager,[18,19] Heidi Thompson,[20] Zeliha Tulek,[21] Kurt Marhardt,[22] and Jan A. Hillert[23]

Correspondence
Dr. Bove
riley.bove@ucsf.edu

Neurol Clin Pract. 2026;16:e200588. doi:10.1212/CPJ.0000000000200588

Abstract

Purpose of Review

As the life expectancy of people with multiple sclerosis (PwMS) increases, the importance of recognizing and addressing specific needs and challenges faced by those undergoing age-related sex hormone changes and hypogonadism is becoming increasingly evident. We present expert-led, practical recommendations from a consensus program that address gaps in age-related sex hormone changes and hypogonadism in PwMS not sufficiently addressed in current literature and guidelines. A multidisciplinary steering committee (SC) of 15 international experts identified 18 key clinical questions across 6 themes: climacteric symptoms in women with MS; impact of MS on the climacteric stage; impact of menopause on MS disease activity and progression; treatment and management of climacteric symptoms in women with MS; late-onset hypogonadism (LOH) in men with MS; and patient-centered care. After thorough review of the evidence from a systematic literature review, the SC formulated 18 clinical recommendations to address the questions. These recommendations were voted on by the SC and an extended faculty of 23 health care professionals from 16 countries, including 2 nurses and 1 patient association representative.

Recent Findings

Consensus was reached when ≥75% of respondents expressed agreement, with a score of 7–9 on a 9-point scale. After a single voting round, all 18 recommendations reached consensus (14 reaching consensus at 90%–100% and 4 at 80%–90%). The clinical recommendations addressed the following: the potential overlap and exacerbation of MS symptoms during the climacteric stage; the need for preventive care and screening during the menopausal transition; the potential for, and a paucity of data on, differential efficacy and tolerability of MS medications in menopausal/postmenopausal women; the complex causal interplay between hormonal and/or immunologic changes and natural aging in PwMS switching to a more progressive phase of disease; consideration of behavioral/lifestyle interventions alongside pharmacologic treatments; effects of hormonal treatments on MS symptoms; and management of LOH in men with MS.

MORE ONLINE

Supplementary Material

Downloaded from https://www.neurology.org by 78.134.103.86 on 30 October 2026

[1]University of California San Francisco Weill Institute for Neurosciences, University of California; [2]Unit of Endocrinology, Department of Medical Specialties, University Hospital and Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Italy; [3]Department of Gynecology, Institut Clínic of Gynecology, Obstetrics and Neonatology, Hospital Clínic of Barcelona, IDIBAPS, University of Barcelona, Spain; [4]Department of Neurology, Institute for Neurological Research, Fleni, Buenos Aires, Argentina; [5]Institute of Biological Chemistry and Physiochemistry (IQUIFIB), CONICET/University of Buenos Aires, Argentina; [6]Katholisches Klinikum Bochum GmbH, Nordrhein-Westfalen, Bochum, Germany; [7]Harvard Medical School, Boston, MA; [8]Brigham and Women's Hospital, Boston, MA; [9]Danish Multiple Sclerosis Center, University Hospital Rigshospitalet, Copenhagen, Denmark; [10]Department of Clinical Medicine, University of Copenhagen, Denmark; [11]Clinic of Reproductive Endocrinology, University Hospital Zürich, Switzerland; [12]Clinical Epidemiology and Biostatistics, School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Sweden; [13]Clinical Epidemiology Division, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden; [14]Department of Epidemiology and Public Health, University College London, United Kingdom; [15]Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Italy; [16]Research Center for Reproductive Medicine, Gynecological Endocrinology and Menopause, IRCCS San Matteo Foundation, Pavia, Italy; [17]Johns Hopkins Medicine, Baltimore, MD; [18]Department of Regional Research, University of Southern Denmark, Odense, Denmark; [19]MS-clinic of Southern Jutland (Aabenraa, Esbjerg, Kolding), Denmark; [20]Southern Health & Social Care Trust, Portadown, Northern Ireland, United Kingdom; [21]Florence Nightingale Faculty of Nursing, Istanbul University-Cerrahpasa, Turkey; [22]Merck GmbH, Vienna, Austria, an Affiliate of Merck KGaA, Darmstadt, Germany; and [23]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden.

The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Copyright © 2026 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.

Summary

These recommendations were based on a robust modified Delphi consensus approach and present a valuable framework for improved patient care. These results emphasize the need to address critical gaps in our understanding and management of PwMS undergoing age-related sex hormone changes and hypogonadism.

Introduction

Multiple sclerosis (MS) remains a leading cause of neurologic disability among young adults (aged 18–40 years).[1] However, advances in early diagnosis and the availability of effective disease-modifying therapies (DMTs) have led to improved quality of life (QoL) and extended life expectancy in MS.[2,3] While MS typically develops before women undergo menopause and men undergo late-onset hypogonadism (LOH),[4-8] most individuals treated according to modern standards transition into these stages while having relatively good neurologic function. As individuals with MS enter these stages, maintaining function and QoL should be highlighted. Therefore, understanding how age-related changes in sex hormones affect people with MS (PwMS) is evidently important. In addition, immunosenescence is associated with a decreased frequency of MS relapses.[9] This evolving profile of disease activity further emphasizes the importance of adapting management strategies to the specific needs of aging PwMS.

Fortunately, management of patients with MS undergoing age-related sex hormone changes, as well as the importance of recognizing and addressing specific needs and challenges they face, is receiving increasing attention in clinical practice.[4,10,11]

In women, the climacteric phase refers to the gradual decline in ovarian function (perimenopause) until cessation of ovarian activity (menopause),[12] representing physiologic changes that mark the transition from reproductive to nonreproductive stages. This transition commonly occurs naturally in women aged 45–55 years.[13] Menopause is diagnosed retrospectively after 12 months of spontaneous amenorrhea. Consequently, the woman is considered to be in the postmenopausal stage.[14] Induced menopause can occur when a woman's menstrual periods end due to medical interventions such as surgical removal of both ovaries or cancer treatments, including chemotherapy or pelvic radiation.[15] Women with MS may face additional challenges on menopause; some menopause-associated symptoms, including depression and anxiety, sleep disturbance, fatigue, bladder problems, and cognitive impairment, can exacerbate or overlap with those of MS.[4,16] Furthermore, studies suggest a potential link between sex hormone levels and the course of MS.[4,11] Increased disability accumulation after menopause has been reported as a potential turning point to a more progressive phase of MS.[17] This could arise from hormonal and/or immunologic changes related to menopause, both of which may increase neuroinflammation and neurodegeneration as a result of aging-associated immunosenescence.[17]

LOH in men is an underdiagnosed condition that typically becomes clinically relevant after 40 years of age.[18,19] LOH is defined by consistently low testosterone levels beyond those seen with normal aging, accompanied by specific clinical symptoms, including loss of libido, erectile dysfunction, reduced muscle mass, increased body fat, anemia, osteoporosis, depressed mood, decreased vitality, sweating, and hot flushes,[20,21] which may have implications for conditions with overlapping symptomatology such as MS.[11,22]

This consensus program aimed to develop expert-led, consensus-based, practical recommendations and opinion statements, focusing on age-related sex hormone changes and hypogonadism in PwMS. These should fulfil an important clinical need by providing expert insights from a patient-centric and multidisciplinary team (MDT) perspective on aspects not sufficiently addressed in existing literature and guidelines.

Methods

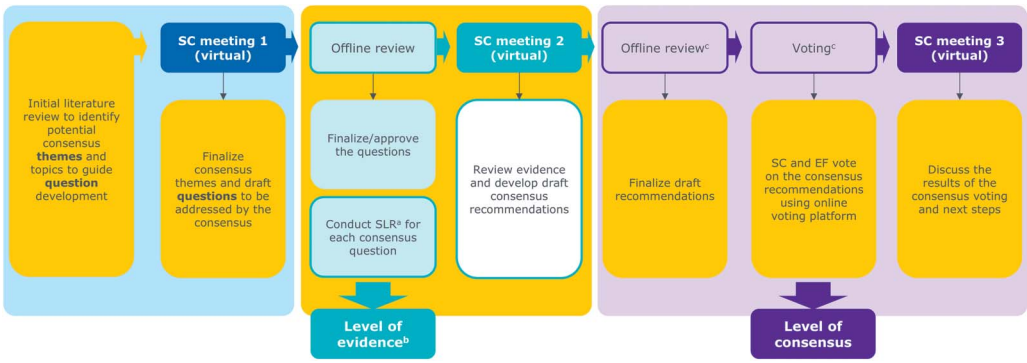
A consensus program, led by a steering committee (SC) comprising an MDT of 15 international clinical experts, was conducted from November 2022 to November 2023. A modified Delphi methodology was used (Figure) to establish consensus across 6 themes: (1) climacteric symptoms in women with MS; (2) impact of MS on the climacteric stage; (3) impact of menopause on MS disease activity and progression; (4) treatment and management of climacteric symptoms in women with MS; (5) LOH in men with MS; and (6) patient-centered care.

The SC initially reviewed published literature focused on these consensus themes, identifying 18 clinical questions (Meeting 1). A systematic literature review (SLR) assessed the importance and eligibility of the questions using the population, intervention, comparison, outcome, and study design framework (eAppendix 1). The identified references during the SLR were quality assessed using the Grading of Recommendations Assessment, Development, and Evaluation rating scale.[23] After thorough review of the evidence, the SC formulated 18 draft clinical recommendations to address the questions (Meeting 2).

To broaden expert input, an extended faculty (EF) of 141 internationally recognized specialists was invited, of whom

Downloaded from https://www.neurology.org by 78.134.103.86 on 30 October 2026

Figure Development of Consensus Recommendations and Voting



[a] Using the PICOS (population, intervention, comparison, outcome, and study design) framework for each question. [b] The level of evidence for each question was based on the number of references that supported each question within the SLR: low (SC feedback and experience), medium (<2 peer-review articles supporting recommendation and/online support [e.g., from congress presentations and society websites]), or high (≥2 peer-reviewed articles supporting recommendations).[23] [c] A single round of voting was deemed sufficient on this occasion. To note, the SC conducted several rounds of amendments to the draft recommendations before the voting stage. In addition, during Meeting 3, all feedback from the voting was reviewed by the SC, with the opportunity to amend recommendations and revote if deemed necessary. This approach aligns with the flexibility described in the literature, noting that modifications to the classical Delphi process, such as reducing the number of rounds or adapting procedures based on study needs, are common and acceptable when rigor is maintained.[e32] EF = extended faculty; PICOS = population, intervention, comparison, outcome, and study design; SC = steering committee; SLR = systematic literature review.

23 participated in the program. The EF was selected based on their clinical expertise, publication records, and SC nominations. The SC developed the consensus framework and drafted the recommendations. The EF participated in validating the draft recommendations through voting using an online platform.

Together, the SC (n = 15) and the EF (n = 23)—representing various specialisms and geographic regions (eTable 1)—contributed to the final consensus agreement scores. Details of the SC and EF selection process are provided in eAppendix 2.

Consensus on each recommendation was achieved when ≥75% of the respondents agreed within the range of 7–9 on a 9-point scale (1 = strongly disagree, 9 = strongly agree). Each recommendation received a "consensus level" (% of votes with scores 7–9 and a "strength" score [median]). Rationale was required for scores ≤6. If respondents felt unqualified to vote on a specific recommendation, they could choose "Not applicable." The voting results were reviewed and discussed during the final SC meeting (Meeting 3).

Standard Protocol Approvals, Registrations, and Participant Consents

This modified Delphi consensus program, funded by Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945), involved the collection of expert opinions for the purpose of developing clinical recommendations. No sensitive or personally identifiable information was collected, and participants' contributions were limited to professional judgments and perspectives. Therefore, this activity would be considered exempt from institutional review board.

Data Availability

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

Results

Altogether, the 18 clinical questions were voted on by 38 participating experts. eAppendix 1 summarizes literature supporting identification of the SLR and detailed outputs for each question. All but 1 SC member voted on all questions; 3 respondents (7.9%) deemed themselves unqualified to vote on ≥1 recommendation and selected "Not applicable." Therefore, the number of experts voting on each recommendation ranged from 34 to 38 participants. After 1 voting round, consensus was achieved for all 18 recommendations: 14 recommendations reached consensus in the 90%–100% range and 4 in the 80%–90% range. eTable 2 lists respondents' rationale for scores ≤6.

The clinical recommendations formulated by the expert SC for addressing specific needs and challenges faced by PwMS undergoing age-related sex hormone changes and hypogonadism are summarized in Table 1 and detailed further.

Theme 1: Climacteric Symptoms in Women With MS

Question 1: How do climacteric symptoms (such as sleep disturbance and lower urinary tract symptoms) overlap with MS symptoms?

Menopausal symptoms can represent a complex challenge in the management of women with MS because many symptoms and/or comorbidities can overlap with existing MS symptoms (Table 2).[4,24,25] Women experiencing climacteric

Downloaded from https://www.neurology.org by 78.134.103.86 on 30 October 2026

Table 1 Expert Recommendations on the Management of Age-Related Sex Hormone Changes and Hypogonadism in People With MS, Themes 1–6

		Consensus level, % of agreement (n/N)[a]	Strength of recommendation, median (mean) score[b]
Theme 1: Climacteric symptoms in women with MS			
CR1	Physicians should be aware of the potential overlap of symptoms and conditions influencing symptoms	97 (37/38)	9 (8.5)
CR2	Women with MS often report worsening of their MS symptoms during the climacteric stage, which can decrease their HRQoL. Physicians should be aware of the potential for climacteric symptoms to exacerbate MS symptoms and evaluate them in a comprehensive, holistic manner, including referrals when indicated	95 (35/37)[c]	9 (8.3)
CR3	Women with MS may not receive all necessary, specific preventive and screening care and should receive the same standard as the general population during the menopausal transition	95 (35/37)[c]	9 (8.4)
Theme 2: Impact of MS on the climacteric stage			
CR4	For most women with MS, the age at which natural menopause occurs does not differ from the general population	100 (37/37)[c]	9 (8.5)
CR5	It is not known whether DMTs are differently tolerated in menopausal women. Climacteric symptoms, particularly VMS, could lead to differences in tolerability	92 (34/37)[c]	8 (8.1)
Theme 3: Impact of menopause on MS disease activity and progression			
CR6	Women who have undergone early or premature menopause may experience worsening in MS-related symptoms	89 (33/37)[c,d]	8 (7.6)
CR7	There is evidence to suggest that the risk of MS relapse may decline after the menopausal age. This may be due to a combination of hormonal changes and natural aging, with patients switching to a more progressive phase of disease. However, more data are needed to confirm causality	95 (35/37)[c]	9 (8.2)
CR8	Significant disability accumulation is often observed after the menopausal age, with patients switching to a more progressive phase of disease	81 (30/37)[c,e]	8 (7.5)
CR9	There is a paucity of data concerning the benefit/efficacy of DMTs in postmenopausal women with MS; most pivotal trials for MS thus far have not included patients aged older than 55 y	100 (36/36)[c,f]	9 (8.7)
Theme 4: Treatment management of climacteric symptoms in women with MS			
CR10	A comprehensive approach to symptom management should be taken for postmenopausal women with MS. Behavioral/lifestyle interventions should be considered alongside pharmacologic treatment	97 (36/37)[c]	9 (8.7)
CR11	Moderate-to-severe VMS during the menopausal age should be screened for and managed according to the most up-to-date guidelines for hormone and nonhormonal therapies in all women with MS	92 (34/37)[c]	9 (8.3)

Continued

Downloaded from https://www.neurology.org by 78.134.103.86 on 30 October 2026

Table 1 Expert Recommendations on the Management of Age-Related Sex Hormone Changes and Hypogonadism in People With MS, Themes 1–6 *(continued)*

		Consensus level, % of agreement (n/N)[a]	Strength of recommendation, median (mean) score[b]
CR12	Moderate-to-severe GSM symptoms during the menopausal age should be screened for and managed according to the most up-to-date guidelines for hormone and nonhormonal therapies in all women with MS	89 (33/37)[c]	9 (8.2)
CR13	More data are needed to evaluate the effects of hormonal treatments on MS symptoms and QoL	97 (36/37)[c]	9 (8.5)
CR14	More research is needed before climacteric-related hormonal therapy can be recommended for neuroprotective benefit in women with MS	97 (36/37)[c]	9 (8.6)
Theme 5: Late-onset hypogonadism in men with MS			
CR15	Limited evidence suggests that men with MS have a higher prevalence of hypogonadism than men without MS	94 (33/35)[c,g]	9 (8.0)
CR16	Symptoms of late-onset hypogonadism should be screened for and managed in all men with MS according to the most up-to-date guidelines for late-onset hypogonadism and hormone therapies	94 (33/35)[c,g]	9 (8.3)
CR17	Testosterone is the primary treatment option for late-onset hypogonadism in men with MS and can be considered in the presence of clinical and biochemical hypogonadism	88 (30/34)[c,h]	8 (7.9)
Theme 6: Patient-centered care			
CR18	In general, anticipatory guidance regarding the interplay of common symptoms and preventive care should be given as part of an integrated approach by the multidisciplinary team. For women with MS, anticipatory guidance should start about 5 y before the typical age of natural menopause (i.e., ∼45 y of age)	95 (35/37)[c]	8 (8.1)

Abbreviations: CIS = clinically isolated syndrome; CR = consensus recommendations; DMT = disease-modifying therapy; GSM = genitourinary syndrome of menopause; HRQoL = health-related quality of life; MS = multiple sclerosis; QoL = quality of life; VMS = vasomotor symptoms.
[a] Percentage of votes with scores 7–9 on a 9-point scale. Participants were provided with the voting option "Not applicable" for recommendations outside their area of expertise. eTable 2 lists the reasons for scoring ≤6.
[b] Median score on a 1–9 scale.
[c] One voter did not cast their vote.
[d] Reasons for the lower score were as follows: 3 voters were concerned about lack of/insufficient evidence, and another voter noted "Weak evidence about that."
[e] Reasons for the lower score were as follows: 4 voters were concerned with lack of supporting evidence. Specifically for the words "significant" and "often"; 4 voters commented on disentangling the attribution of effect of menopause from the effect of age and disease duration; and 1 voter noted "Data from our CIS cohort indicate that aging and not hormonal changes seem to be the main driver. Menopause does not modify disability trajectories in a longitudinal cohort of women with CIS and MS followed from disease onset. Otero-Romero S, et al. Eur J Neurol. 2022; 29(4):1075–1081."
[f] One voter selected "Not applicable."
[g] Two voters selected "Not applicable."
[h] Three voters selected "Not applicable."

and MS symptoms often report poor sleep, mood changes or depression, fatigability, urinary and sexual dysfunction, and lower health-related QoL (HRQoL).[4,25]

Question 2: How do climacteric symptoms (such as vasomotor symptoms and mood changes) exacerbate or mask MS symptoms and vice versa?

During menopause, approximately half of patients report worsening of MS symptoms,[10] and perimenopausal changes, such as hot flashes or sleep disturbance, can exacerbate certain MS symptoms (Table 2).[24] Women with MS may experience fewer relapses after menopause, but some MS symptoms may worsen as estrogen levels decline during this period.[27] Notably, women receiving menopause hormone therapy (HT) have reported improvement in their MS symptoms during menopause (eTable 3),[10] and HT remains the most effective treatment for vasomotor symptoms (VMS) (eTable 4).[26]

Perimenopause is also a vulnerable period often associated with the onset or worsening of affective symptoms such as

Downloaded from https://www.neurology.org by 78.134.103.86 on 30 October 2026

Table 2 Overlap and/or Exacerbation of Climacteric, Postmenopausal, and MS Symptoms: Examples and Suggested Therapeutic Interventions

Category/symptoms	Example	Behavioral/lifestyle interventions	Pharmacologic treatment
Fatigue	• Fatigue, or lassitude, is one of the more debilitating symptoms of MS[24] • Often correlates with disease duration and is out of proportion to the degree of physician-detected impairment or energy expenditure[24] • During perimenopause, fatigue tends to increase in severity and frequency and may require intervention[24] • Fatigue in patients with MS could increase in severity and frequency during menopause, limiting daily activities. In these patients, fatigue can be multifactorial, complicated by VMS (e.g., hot flashes), potentially causing the Uhthoff phenomenon and symptomatic exacerbations[17,24]	• Rule out additional contributors, such as thyroid disease[24] • Management of contributing factors: VMS, affective symptoms, sleep quality, spasms, and pain[24] • Screen for restless leg syndrome and obstructive sleep apnea[24] • Avoid caffeine after lunch and alcohol near bedtime[24] • Review daily schedule: encourage spacing work routines to allow time for intermittent rest breaks throughout the day, maximize essential activities in the morning, when patients generally feel more alert[24] • Mind-body techniques, such as relaxation and meditation practices, can help reduce stress and decrease fatigue[24]	• Wakefulness promotion (modafinil, amantadine)[24] • SSRIs (fluoxetine or others)[24] • Stimulants (methylphenidate)[24]
Urinary	• Postmenopausal women may experience bladder irritability and incontinence, and an increased risk of urinary tract infections[24] • These symptoms may be magnified in those MS patients with baseline bladder dysfunction[24]	Bladder training[24] • Frequent voluntary emptying (e.g., start with every 2 h) to keep the bladder volume low • Pelvic floor physical therapy and exercises • Biofeedback, posterior tibial nerve stimulation	• Antimuscarinics (oxybutynin, tolterodine, fesoterodine)[24] • Beta-3 adrenergic receptor agonists (mirabegron) • Antispasmodics (baclofen, tizanidine)[24] • Local estrogen may help with genitourinary syndrome of menopause[e33] • Local estrogen, or antibiotic prophylaxis, may be utilized in patients with higher disability to prevent UTIs[24]
Affective	• Depression influences the severity of other MS symptoms; for example, it is a strong predictor of cognitive dysfunction[24] • Perimenopausal women may experience depression but also anxiety, irritability, and rage[24]	• Psychotherapy[24] • Support groups[24] • Fatigue and sleep optimization[24] • Social management of work and familial stressors[24]	• Antidepressants (fluoxetine, sertraline, escitalopram, citalopram, venlafaxine, bupropion)[24]
Cognitive	• Approximately one-half of patients with MS experience some degree of cognitive impairment[24] • During perimenopause, women report changes in attention, executive function and multitasking, word-finding difficulties, and memory[24] • Women with MS may experience distress from perceived cognitive changes[24]	• Neurocognitive testing may help to identify particular areas of dysfunction[24] • Cognitive rehabilitation (formal or informal) to develop organizational strategies (e.g., keeping lists, simplifying daily schedule, and maximizing "good" time)[24] • Addressing sleep (night sweats, restless leg syndrome), fatigue, mood, and pain may help with cognitive symptoms[24]	
Vasomotor (hot flashes [including night sweats], cold flashes, vasomotor instability, rapid heartbeat)[24]	• Women with MS may have difficulty distinguishing whether some symptoms are due to MS flare-ups or menopause. Some women seek immediate neurology consultations, while others may wait to seek health care and assume the symptoms are typical of menopause[24] • Perimenopausal changes such as hot flashes or sleep disturbance can further worsen certain MS symptoms[24] • VMS can start in women during perimenopause and last for approximately 7 y or longer, influencing their QoL and potentially affecting cardiovascular, bone, and brain health[26]	• Air conditioning, cool drinks[24] • Avoidance of hot/spicy foods[24] • Swimming[24] • Cooling vests or collars[24] • Weight loss[24] • Smoking cessation[24] • Acupuncture[24] • Hypnosis[24]	• HT (estrogen alone or combined with progestogen)[26] • Fezolinetant (FDA approved) is an NK3 receptor antagonist for the treatment of VMS associated with menopause[e3,e10,e34] • Antiepileptics and antidepressants: gabapentin/pregabalin, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, venlafaxine, desvenlafaxine[24]

Continued

Downloaded from https://www.neurology.org by 78.134.103.86 on 30 October 2026

Table 2 Overlap and/or Exacerbation of Climacteric, Postmenopausal, and MS Symptoms: Examples and Suggested Therapeutic Interventions *(continued)*

Category/symptoms	Example	Behavioral/lifestyle interventions	Pharmacologic treatment
Sexual dysfunction (e.g., decreased libido/arousal, atrophic vaginitis, and inadequate vaginal lubrication)[25]	• In women, MS spinal cord lesions are highly associated with disturbances in genital sensation, arousal, and orgasm[24] • Occasionally, perimenopausal breast tenderness may be mistaken for sensory issues in the thoracic regionl[24] • Somatic symptoms may be compounded by decreased self-esteem or body image, changes in physiologic function, concern about bladder symptoms, and decreased intimacy and interpartner communication[24]	• Decreased sensation: vibrators and other devices may increase stimulation[25] • Patient education and guided counseling, such as body mapping techniques or pelvic floor exercises, can increase arousal, orgasmic response, intimacy, and couple communication[25] • Vaginal dryness: lubricants[25] • Counseling focused on sexual feelings, communication, and attitudes that interfere with sexual enjoyment[25] • Couples' education/counseling: focused on mutual support, communication, stress, and anger management[25]	• HT (systemic or low-dose vaginal)[26] • Paresthesia—antiepileptic drugs: carbamazepine, gabapentin[25] • Local estrogen may help with genitourinary syndrome of menopause[e33]
Sleep	• Sleep disturbances are more prevalent in patients with MS than in the general population and are more common in women with MS than in men with MS[4] • After menopause, the risk of sleep apnea increases in women[e35]	• Sleep hygiene (avoid caffeine after lunch and alcohol near bedtime)[24] • Avoid smoking[24] • Weight loss[24] • Air conditioning, cool room[24] • Mood and anxiety management[24] • Phototherapy[24] • Bladder regimen: minimize fluid intake in the evening[24] • Evaluation for sleep apnea and consideration of CPAP[e36]	• Benzodiazepines (triazolam, estazolam, lorazepam, temazepam)[24] • Nonbenzodiazepines: hypnotics (zaleplon, zolpidem, eszopiclone, ramelteon, doxepin)[24]
Pain syndromes	• After menopause, women may experience arthralgias, myalgias, and musculoskeletal pain[24] • Hormonal changes may also impact pain processing pathways, immune cells, and chondrocytes[24] • Cervical and lumbar spondylosis, osteopenia, joint immobility, spasticity, and deconditioning due to MS-related weakness may magnify these concerns[24] • Musculoskeletal and neuropathic pain are frequently exacerbated at menopause[24]	• Evaluation for bone density loss: osteopenia or osteoporosis[24] • Evaluation for rheumatologic disorders[24] • Physiotherapy and massage to improve joint mobility and spasticity[24] • Weight management, exercise[24]	• Pain triggered by spasticity: baclofen (consider intrathecal baclofen for severe pain), diazepam, dantrolene, tizanidine[24] • Neuropathic pain and paresthesias: phenytoin, carbamazepine, TCAs (amitriptyline and nortriptyline), gabapentin and pregabalin, duloxetine[24] • Musculoskeletal pain: integrated approach at a pain center[24]
Osteoporosis	• Osteoporosis risk is increased post-menopause, which is additive to the increased risk in MS due to disability/mobility problems and long-term steroid use[e37,e38]	• Calcium and vitamin D supplements[e39] • Protein intake[e39] • Probiotics[e39] • Physical activity and exercise[e39] • Fall prevention[e39]	HT[e39]
Other	• Smoking and menopause are associated with MS disease course, including the onset of relapse and progressive MS in women[e40]	• Counseling patients with MS on smoking cessation, especially in women who experience premature or early menopause[e40]	

Abbreviations: CPAP = continuous positive airway pressure; FDA = Food and Drug Administration; HT = hormonal therapy; MS = multiple sclerosis; NK3 = neurokinin 3; QoL = quality of life; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; UTI = urinary tract infection; VMS = vasomotor symptom.
Perimenopause typically emerges in mid-40s and is associated with menopausal symptoms. Menopause is confirmed when menstrual periods are absent for 12 months consecutively. Postmenopause is defined as the years after menopause.

anxiety and depression.[17] Experiences during the climacteric phase may worsen because of age-related increases in disability, progression in MS severity marked by accelerated brain volume loss and neurodegeneration, and declining levels of protective ovarian hormones, and loss of lean body mass, all contributing to further disability progression.[28,29]

Thus, menopausal and MS symptoms, as well as their overlapping effects, may affect the HRQoL of menopausal

Downloaded from https://www.neurology.org by 78.134.103.86 on 30 October 2026

patients with MS who are already enduring a stressful period, with multifaceted implications for their lives.[17,30]

Question 3: Which specific preventive and screening measures should be recommended for postmenopausal women with MS?

Breast cancer screening can be challenging for women with MS because of transportation or mobility issues, discomfort during examinations, negative attitudes from health care providers, forgetfulness, fear, and feeling overwhelmed.[31] To increase screening rates, health care providers should proactively address these barriers.[31] Postmenopausal women with MS should be encouraged to undertake preventive and screening measures such as magnetic resonance imaging, laboratory tests, neurologic evaluations, and assessments of disease severity (Table 3).

Current international MS treatment guidelines do not provide unified recommendations for adjusting clinical or imaging monitoring after menopause, although the literature supports the need for further research and individualized management strategies.[4] Table 3 summarizes existing guidelines and helps bridge international recommendations and practical implementation strategies for aging women with MS.

Given the increased cardiovascular risk during the perimenopausal and postmenopausal periods[33] and the potential association of cardiovascular disease with reduced brain volume and disability progression in PwMS,[4,34,35] future clinical guidelines for MS should include recommendations for enhanced cardiovascular risk screening, preventive measures, and consideration of HT in women at raised risk.[36]

Theme 2: Impact of MS on the Climacteric Stage

Question 4: How does the age of natural menopause in women with MS compare with the age of natural menopause in the general population?

There are similarities in the age of natural menopause between those with MS (~48–52 years) and the general population (~49–53 years).[36-38] Although MS has not been associated with the average age at menopause, some medications (e.g., methylprednisolone, interferon beta, cyclophosphamide, and mitoxantrone) may affect menopausal age.[36,39,40] The Stages of Reproductive Aging Workshop (STRAW +10) criteria provide a consistent framework for defining menopausal stages, enabling more accurate comparisons between women with MS and the general population regarding the age at natural menopause.[41]

Table 3 Routine Screening and Monitoring Measures Recommended for Postmenopausal Women With MS

Test	Screening parameter
Imaging	MRI of the brain and spinal cord[48,e20,e41-e43]
	Dual-energy X-ray absorptiometry (DEXA)[e44]
	Mammogram (X-ray)
	Overall risk of postmenopausal breast cancer was 13% higher among patients with MS (n = 19,330) compared with women without MS (n = 193,458) in a Swedish general population-based cohort study (1968–2012)[e45]
Laboratory tests	Analytic tests (blood and urine)[e44]
	Vitamin D level and bone turnover markers[e44,e46]
	Immunoglobulin G oligoclonal band examination (at diagnosis)[32]
	Estradiol, LH, FSH, 17-OH progesterone, prolactin, TSH, insulin-like growth factor-1, ACTH, and cortisol[e20,e43]
Evaluation by neurologist	Clinical interview and evaluation by the neurologist[e20,e41,e44]
Patient-reported symptoms	Frequency of VMS[e20]
	Menopausal symptoms (MENQOL)
	Frequency of VMS[e19]
	Sleep (Insomnia Severity Index)[e20]
	Mood (e.g., Beck Depression Inventory)[e20]
Disease severity	Expanded Disability Status Scale[e20]
	Dexterity: 9-Hole Peg Test[e48]
	Paced Auditory Serial Addition Test[e20,e48] or Symbol Digit Modalities Test[e20]

Abbreviations: ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MENQOL = Menopause-Specific Quality of Life questionnaire; MS = multiple sclerosis; TSH = thyroid-stimulating hormone; VMS = vasomotor symptoms.

Downloaded from https://www.neurology.org by 78.134.103.86 on 30 October 2026

Question 5: How do DMTs and their side effects affect climacteric symptoms in women with MS?

DMTs do not seem to significantly affect menopausal symptom severity in women with MS.[42] Chemotherapy drugs (e.g., cyclophosphamide or mitoxantrone) may elevate amenorrhea risk in women with MS, potentially leading to premature ovarian failure and affecting reproductive capacity.[24,39,43] Data on this topic are sparse and warrant further investigation where generation of real-world evidence will be crucial.

Theme 3: Impact of Menopause on MS Disease Activity and Progression

Question 6: How does an early (<45 years) or premature (<40 years) menopause affect MS symptoms and disease course, such as the risk of relapse and disability worsening?

Early menopause, often a consequence of surgical menopause or DMT use, may have implications for the onset and progression of MS.[36,38,44,45] However, no conclusive evidence suggests that early or premature menopause can lead to symptomatic progression related to MS. In a study investigating the patient-reported impact of menopause through a large online research platform for patients with MS, surgical menopause was found to be associated with significantly higher HT use than natural menopause and women who experienced menopause at an earlier age had worse patient-reported severity scores.[44]

Question 7: How does MS inflammatory activity (including relapse rate) change during and after the menopausal age?

Hormonal changes during menopause, particularly decreases in estrogen levels, might lead to altered inflammatory activity in MS, signaling potential transition to a more progressive disease stage.[46] Women with MS often experience higher inflammatory disease activity and relapse rates than men.[17] However, after 50 years of age, differences between sexes in relapse rate dissipate but disability progression worsens.[17] These findings suggest that the observed differences in disease activity may be associated with menopausal hormone changes.

Studies have reported a decrease in postmenopausal relapse rates in women with MS compared with the perimenopausal period.[17,27,47] However, disability tends to worsen after menopause, which may arise from hormonal and immunologic changes affecting inflammation and neurodegeneration.[17]

Question 8: How does MS disease progression change during and after the menopausal age?

Some studies indicate a potential link between menopause and disability progression[47,48] while others do not.[27,32] Disability often progresses around menopausal age; whether it is a consequence of menopause or aging remains unclear.[32] To address this uncertainty, it is crucial to consider the stage of the menopausal transition when assessing studies.[41] Ideally, longitudinal studies can provide definitive answers to the question of menopause (reproductive aging) vs chronological or biological aging. More data are needed to understand how menopause and age-related immune changes may influence MS exacerbations and disability progression during the climacteric phase.

Question 9: What data gaps exist around the benefit/efficacy of DMTs in postmenopausal women with MS?

Currently, no studies have specifically examined the effects of DMTs in women with MS after menopause. However, after adjusting for potential confounders, disability progression was determined to be independent of relapses, regardless of any changes in DMT use.[27,49] Several data gaps persist regarding DMT effectiveness in postmenopausal women with MS, including the absence of clinical trial data, the lack of real-world data evaluating the effectiveness and safety considerations (e.g., vaccine response or infections) of DMTs, and the scarcity of guidance and information on pharmacokinetics and pharmacodynamics in this patient population.

A closely linked theme that must be appraised concurrently when considering DMT use in postmenopausal women is the impact of aging in general. With advancing age, the MS disease course may shift from an inflammatory to a nonactive progressive neurodegenerative phenotype, for which current DMTs are only partially effective and the benefit-risk ratio may not always support continued treatment.[50,e1,e2] In this context, recommendations related to immunosenescence can be particularly valuable for guiding clinical decisions on treatment de-escalation or switching.

Theme 4: Treatment and Management of Climacteric Symptoms in Women With MS

Question 10: What treatment options are available for women with MS to enable a comprehensive approach to climacteric symptom management (e.g., sleep, mood, pain, lower urinary tract symptoms, cognition, fatigue, and hot flashes)?

Managing climacteric symptoms in women with MS often requires a multifaceted approach because of the complex interplay between MS symptoms and those associated with menopause. Management approaches for menopausal symptoms include behavioral/lifestyle interventions (e.g., mindfulness and dietary supplements), menopausal HT (estrogen alone or in combination with progestogen), and non-HT (e.g., antidepressants and neurokinin 3 [NK3] receptor antagonists fezolinetant [where available] or elinzanetant [in Phase III]). Fezolinetant is approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of moderate-to-severe VMS due to menopause. As of September 2024, fezolinetant is not included in the guidelines because of its recent approval.[4,25,e3-e5]

Evidence on the impact of HT on mood in postmenopausal women without depression varies. HT can provide menopausal symptom relief and improve HRQoL.[17] However, its impact on MS progression and its long-term consequences remain

Downloaded from https://www.neurology.org by 78.134.103.86 on 30 October 2026

unknown.[17] Two studies (a Danish nationwide registry and a longitudinal United States–based study) found no significant effect of menopause HT on disability progression.[45,e6]

The North American Menopause Society—now called The Menopause Society—recommends personalized HT with the lowest dose and for the shortest duration possible.[17] The International Menopause Society suggests HT as first-line treatment for the management of climacteric symptoms, with the duration of treatment based on a shared decision-making process.[e7] The risks and benefits associated with the use of HT are listed in eTable 3.

Question 11: What treatment options are available to manage moderate-to-severe VMS in women with MS, and do they differ from the treatments available for the general population of menopausal women?

Management of VMS in women with MS typically follows general approaches used for menopausal symptoms in women without MS, involving a combination of non-pharmacologic and pharmacologic strategies. Flexibility and adaptability are at the core of the most relevant guidelines in menopause, which prioritize individualized approaches over rigid, one-size-fits-all methodologies (eTable 4).

Estrogen therapy with or without a progestogen is the most effective treatment of menopause-related VMS and remains the primary indication for moderate-to-severe VMS.[e8] Health care professionals should be aware of non-HT options for women for whom menopause HT is not suitable because of contraindications (e.g., estrogen-dependent cancers or cardiovascular disease) or personal preferences.[e9] Antidepressants can be used to treat VMS,[53] and NK3 receptor antagonists (e.g., fezolinetant, where available) represent a promising new class of drugs for managing menopausal symptoms,[e10] offering potential benefits over traditional HT. However, the specific impact of NK3 receptor antagonist on women with MS during menopause remains an important area for future research.

One study in women with VMS suggested that mood may improve with HT but worsen with progestogens, especially in women with a history of premenstrual syndrome, premenstrual depressive disorder, or clinical depression.[e8]

In the United States, the combination of bazedoxifene and conjugated equine estrogens is approved for the treatment of moderate-to-severe VMS associated with menopause and for the prevention of postmenopausal osteoporosis.[e11] Bazedoxifene is also marketed as monotherapy in Italy, Spain, and Japan.[e11]

Tibolone is an HT classified as a selective tissue estrogenic activity regulator and is approved by the EMA for the treatment of estrogen-deficiency symptoms in postmenopausal women more than 1 year after menopause.[e12,e13] It is emerging as a potential therapeutic candidate in MS because of its neuroprotective and anti-inflammatory properties.[e12,e14]

Question 12: What treatment options are available to manage moderate-to-severe genitourinary syndrome of menopause symptoms in women with MS, and do they differ from the treatments available for the general population of menopausal women?

Genitourinary symptoms are highly prevalent and significantly affect menopausal women.[e15-e17] Genitourinary syndrome of menopause (GSM) is likely underdiagnosed and undertreated, but symptoms can be effectively managed.[e18]

Currently, no specific guidelines solely focus on managing GSM in women with MS (eTable 5). HT remains the most effective treatment for moderate-to-severe GSM,[e9,e18] because of its effectiveness in restoring urogenital tissue health by compensating for the decline in estrogen levels.[e15-e17] Safe and effective options include low-dose vaginal estrogens, vaginal dehydroepiandrosterone (DHEA), estrogen agonist/antagonist ospemifene (ospemifene is approved by the FDA for the treatment of moderate-to-severe dyspareunia due to menopause) (where available), and systemic estrogen therapy (specifically after hysterectomy).[e18,e19] Long-term studies (>52 weeks) on the endometrial safety of vaginal DHEA and ospemifene are lacking.[e18]

Question 13: What evidence suggests that climacteric-related HT affects MS symptoms and QoL?

Some studies have indicated that HT did not affect MS symptoms or the overall disease course,[e20,e21] while others reported improvements in MS disease severity and HRQoL.[28,e22,e23] It is unclear whether HT directly improves physical HRQoL or whether women with better physical HRQoL tend to receive age-appropriate medical care, potentially contributing to their improved HRQoL.[e24] Further research is required to comprehensively understand the impact of HT on this population.[25]

Question 14: What is the evidence to suggest that climacteric-related HT has a neuroprotective effect for women with MS?

The neuroprotective effects of climacteric-related HT in women with MS remain unknown. Estrogens have been suggested to play a role in altering immunomodulation in MS and potentially offer neuroprotective effects.[e22] A pilot, open-label study (N = 10) suggested that testosterone supplementation might act as a neuroprotective and remyelinating therapy for men with relapsing-remitting MS and testosterone deficiency.[e25] Well-controlled clinical studies are necessary to establish efficacy, safety, and appropriate use of HT for neuroprotection in women with MS.

Theme 5: LOH in Men With MS

Question 15: Is there any evidence to suggest that LOH in men with MS occurs at an earlier age and/or with a greater androgen decline compared with men in the general population?

No clear or consistent evidence currently indicates that LOH occurs earlier or with a greater decline in androgen levels in men with MS compared with the general male population. A small observational study reported a high prevalence of hypogonadism in men with MS[e26] while others noted decreased testosterone

Downloaded from https://www.neurology.org by 78.134.103.86 on 30 October 2026

levels in men with MS relative to healthy controls.[7,e27] Research exploring hypogonadism timing and prevalence in men with MS compared with appropriate controls is needed.

A role for hypogonadism in the development of MS in men has been proposed based on data indicating that hypogonadism precedes MS or presents early in the MS disease course,[e24] combined with the fact that men tend to develop MS when androgen levels naturally decline.[7,e24] Small cohort studies have also indicated a possible link between low testosterone, increased inflammatory markers, and disease severity but do not provide conclusive evidence of increased relapse rates.[7,22,34]

Evidence suggests that testosterone may exert neuroprotective and immunomodulatory effects,[4,34,35] potentially reducing inflammation and promoting neural repair. These potential protective mechanisms provide further rationale for considering testosterone replacement in men with MS and comorbid LOH.

Evidence on the immunologic role of testosterone in MS is limited; this area should be considered a research priority for future studies focused on men with MS.

Question 16: How should symptoms of LOH (e.g., bladder dysfunction, fatigue, sexual dysfunction, lowered libido, and weakness) be screened for and managed in men with MS?

Managing LOH in men with MS remains challenging because of the absence of specific guidelines for PwMS and the existence of conflicting recommendations (eTable 6).[e28] Diagnosis relies on symptoms, signs, and laboratory tests while lifestyle changes combined with testosterone treatment offer symptomatic relief for LOH.[e28] European and North American guidelines recommend measuring total testosterone as the first step of managing LOH, but the biochemical cutoff value for total testosterone varies.[e29] Low levels of testosterone and/or estradiol in PwMS have been linked to higher disability scores and cognitive decline, as revealed by screening tools such as the Symbol Digit Modalities Test and Expanded Disability Status Scale.[e27]

PwMS can be screened for hypogonadism symptoms using the Androgen Deficiency in Aging Males Questionnaire; positive results may require additional testosterone measurement tests.[e26] LOH symptoms may overlap with the effects of aging, which can worsen motor disability, cognitive decline, fatigue, and psychiatric symptoms associated with MS,[7] making assessments challenging. Thus, men with signs of LOH should be referred to specialists (e.g., andrologists, endocrinologists, or neurologists).

Question 17: What treatments are available to manage symptoms associated with LOH in men with MS, and when should treatment be considered?

Treatment should be implemented according to the most up-to-date guidelines for HT (eTable 6).

The effectiveness of testosterone in treating LOH has been demonstrated, and testosterone replacement therapy (TRT) is indicated in men aged 40 years or older with signs and symptoms of LOH.[e29] Managing comorbidities, such as diabetes and hypertension, and improving patients' lifestyle is important when providing TRT.[e29]

Theme 6: Patient-Centered Care

Question 18: What are the key points related to the climacteric stage in women and LOH in men that should be discussed with PwMS? When should the discussion take place?

No specific clinical guidance is available on when and how to discuss the climacteric stage and LOH with women and men with MS, respectively. However, the importance of discussing symptoms that can overlap with or exacerbate MS should not be underestimated.

MS neurologists typically identify and address overlapping or worsened symptoms associated with the menopausal transition.[24] While careful clinical examinations and magnetic resonance imaging can help distinguish between relapses and pseudo-relapses, addressing individual symptoms can provide significant relief (Table 2).[24]

Neurologists and other MS clinicians (e.g., primary care physicians and gynecologists) should collaborate to manage climacteric symptoms and prevent complications.[24] The menopausal transition requires thorough evaluation of MS-related, hormonal, and lifestyle factors.[e24] Careful selection of medications and frequent review of side effects are essential to prevent polypharmacy complications, necessitating an integrated approach to care that considers the interplay between symptoms of MS and menopause.[24]

For LOH, symptoms guide the decision for TRT, where low testosterone levels aid diagnosis. Managing diabetes and hypertension and improving lifestyle are important during TRT.[e29]

Discussion

The clinical recommendations and opinions provided here were carefully developed by an expert SC to complement existing guidelines regarding management of age-related sex hormone changes and hypogonadism that could be applied to PwMS. The strength of this consensus program lies in its expert panel of 38 specialists from various disciplines, ensuring a robust process with valuable multifaceted perspectives. The recommendations underwent a thorough development process involving multiple rounds of review and discussion, enhancing quality and value. The recommendations aim to resolve uncertainties and inconsistencies in clinical practice, emphasizing the importance of guiding and standardizing patient care. All recommendations achieved a high consensus rate (80%–100%).

Downloaded from https://www.neurology.org by 78.134.103.86 on 30 October 2026

The topics for which consensus was lowest among the expert panel were associated with a lack of and/or conflicting evidence (eTable 2 outlines any concerns raised during voting). Consensus recommendation (CR) 8 on postmenopausal disability progression had the lowest agreement rate (81%; Table 1). The lack of supporting evidence and difficulty in separating the effects of menopause from those of age and disease duration were divisive and reflected the complexity of disentangling the effects of reproductive aging from chronological and biological aging that occur concurrently.[32] Further studies are necessary to comprehensively understand the underlying reasons for disability progression in women after menopause. There is also a lack of robust scientific evidence on worsening of MS symptoms in women who undergo early menopause (CR6, 89% agreement). The SC emphasized the need for further research on this because there is ample anecdotal and patient-reported evidence. Given overlapping symptoms, exploring potential hormonal links in patients with primary ovarian insufficiency or early menopause is important. Collaborating with gynecologists to examine HT options could improve symptom management in this patient population.

The relationship between aging, hormones, immunologic changes, and overlapping symptoms associated with menopause, MS, and comorbid conditions is complex. Attributing causality is challenging and underscores the importance of individualized and interdisciplinary management of patients and symptoms. Most MS clinical trials exclude patients older than 50 years because younger individuals both experience more relapses and fewer comorbidities, improving the study of DMT effects. Such trials prioritize statistical power but overlook crucial aging and immunomodulation concerns. Further research and real-world evidence are needed for the aging MS population.

Tailored management of climacteric symptoms in women, including those with MS, is crucial. Guidelines recommend assessing individual risks and benefits of treatment options rather than using a one-size-fits-all approach. eTables 5 and 6 summarize the latest guidelines for managing climacteric symptoms. Anticipatory guidance is crucial in preventive care for women with MS. It should begin 5 years before natural menopause (CR18). However, time constraints in clinical settings may affect feasibility of recommendation implementation. Regardless of age, women should promptly consult a doctor regarding symptoms and have regular gynecologic check-ups.

Scientific panel member recommendations included more frequent cervical screening for women on high-efficacy DMTs, given possible increase in cervical dysplasia associated with moderate-efficacy and high-efficacy DMT use.[e30] Another study indicated concerns about heightened cancer risks for patients with MS associated with specific treatments or factors.[e31] These observations underline the need for close monitoring, vigilant screening practices, and ongoing research to better understand and mitigate potential risks associated with specific MS treatments and their impact on women's health.

This program has potential limitations. First, reliance on professional networks and publicly available information for selecting participants may have introduced selection bias and limited global representation. Second, diverse clinical expertise was included, although future efforts could benefit from additional patient perspectives. Third, multiple rounds are common in Delphi studies; however, given the focused scope of this program and high level of initial agreement among participants, a single round was deemed sufficient. Fourth, current literature and available data on MS management largely focus on binary gender categories, with limited or no specific information regarding gender-diverse individuals. Limited consideration of sex and gender diversity as critical variables in neurologic research underscores a substantial clinical and research gap, highlighting the need for more inclusive clinical guidelines. Further research is needed to understand the disease course, management strategies, and age-related changes in all patient populations. Another limitation is insufficient data, hindering comprehensive and/or practical recommendations in certain areas. Finally, tailored clinical guidelines for PwMS with menopause or hypogonadism are lacking, limiting our ability to make more definitive statements about the challenges and complexities arising from the MS-menopause-hypogonadism intersection. Consequently, owing to the lack of data, it is difficult to make definite evidence-based recommendations.

Conclusions

An international SC of MS and/or gynecology experts, along with a diverse EF, reached high consensus on recommendations and opinion statements, addressing critical gaps in the impact and management of age-related sex hormone changes and hypogonadism in PwMS. These recommendations provide a valuable framework to support clinicians in optimizing patient care, highlight the urgent need for additional research to address critical knowledge gaps, and underscore the importance of multidisciplinary collaboration, particularly between neurologists and gynecologists, essential to providing integrated care for PwMS in clinical practice.

Acknowledgment

Ana María Rodríguez de Ledesma and Wendy Haywood of Bedrock Healthcare Communications provided medical writing support, funded by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945). Assistance with the systematic literature review was provided by AccuScript and supported by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945). The SC thanks all the experts who contributed their knowledge to this

Downloaded from https://www.neurology.org by 78.134.103.86 on 30 October 2026

TAKE-HOME POINTS

- Eighteen clinical recommendations were developed through a modified Delphi consensus process involving an international committee of gynecologists, endocrinologists, and multiple sclerosis (MS) specialists.
- The process identified key gaps in understanding and management of people with MS (PwMS) undergoing age-related sex hormone changes and hypogonadism.
- The recommendations provide practical insights from an expert multidisciplinary team perspective.
- These recommendations aim to support clinicians in improving care of PwMS, while highlighting research needs and closer interprofessional collaboration between neurologists, gynecologists, internists, and rehabilitation experts.

program by voting on the draft recommendations. Listed below are 23 extended faculty members and patient advisory groups who consent to being acknowledged in this document: Aksel Siva, from Istanbul University-Cerrahpasa, Istanbul, Turkey; Amanda Montgomery, from Multiple Sclerosis Association of America, Cherry Hill, NJ; Amy Perrin Ross, from Loyola University Medical Center, Maywood, IL; Anne Cross, from Washington University, St Louis, MO; Anneke Van Der Walt, from Monash University, Australia; Annette Okai, from North Texas Institute of Neurology and Headache, Frisco, TX; Elisabeth Gulowsen Celius, from Oslo University Hospital, Oslo, Norway; Jiwon Oh, from Temerty School of Medicine - University of Toronto, and St. Michael's Hospital, Toronto, Canada, Seoul National University, Seoul, South Korea, and Johns Hopkins University, Baltimore, MD; Joanna Kitley, from University Hospital Southampton, Southampton, United Kingdom; Jürg Kesselring, from Kliniken Valens, Valens, Switzerland; Klaus Schmierer, from Queen Mary University of London, London, United Kingdom; Kristen Krysko, from University of Toronto, Toronto, Canada; Mar Tintoré, from Autonomous University of Barcelona, Hospital Universitari Vall d'Hebron, Barcelona, Spain; Marcelo Moccia, from University of Naples Federico II, Naples, Italy; Maria Pia Sormani, from University of Genoa, Genoa, Italy; Marinella Clerico, from University of Turin, Turin, Italy; Rhonda Voskuhl, from University of California-Los Angeles, Ronald Reagan UCLA Medical Center, Los Angeles, CA; Sarah Morrow, from London Health Sciences Centre University Hospital, Western University, and Lawson Health Research Institute, Schulich School of Medicine & Dentistry, ON, Canada; Tatjana Pekmezovic, University of Belgrade, Belgrade, Serbia; Thomas Berger, from Medical University of Vienna, Vienna, Austria; Uwe Zettl, Universitatsmedizin Rostock, Rostock, Germany; Vilija Jokubaitis, from the University of Melbourne and Monash University, Melbourne, Australia; and, Joep Killestein, from Amsterdam UMC, Amsterdam, Netherlands.

Author Contributions

R. Bove: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M. Simoni: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. C. Castelo-Branco: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. J. Correale: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. K. Hellwig: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M.K. Houtchens: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M. Magyari: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. G. Merki-Feld: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. S. Montgomery: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. R.E. Nappi: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. W. Shen: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. E. Stenager: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. H. Thompson: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. Z. Tulek: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. K. Marhardt: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. J.A. Hillert: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

Study Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945), who provided funding for the project, but had no input into the development of clinical questions or recommendations. No company representative voted on the recommendations. The authors received no financial support for the authorship and/or publication of this article.

Downloaded from https://www.neurology.org by 78.134.103.86 on 30 October 2026

Disclosure

R. Bove has received research support from the US Department of Defense, NIH, and National MS Society, as well as Biogen, Novartis, and Roche Genentech, and consulting and advisory board fees for Alexion, Biogen, EMD Serono (Billerica, MA), Janssen, Sanofi, Novartis, Roche Genentech, and TG Therapeutics. M. Simoni has received honoraria for lectures, advisory boards, and research grants from the healthcare business of Merck KGaA, Darmstadt, Germany, and Ferring. C. Castelo-Branco has received research support from the MCIN, European Union, Instituto de Salud Carlos III (Spain), Deka, Procare, and Interpharma and consulting, lecturer, and advisory board fees from Theramex; Shionogi; Organon; the healthcare business of Merck KGaA, Darmstadt, Germany; and Pierre Fabre. J. Correale has received compensation for academic presentations, participation in advisory councils, and assistance to attend congresses from Biogen; the healthcare business of Merck KGaA, Darmstadt, Germany; Novartis; Roche; Bayer; Sanofi-Genzyme; Gador; Raffo; Bristol Myers Squibb; and Janssen. K. Hellwig has received personal compensation as a speaker/consultant from Bayer; Bristol Myers Squibb; Biogen; INC research; the healthcare business of Merck KGaA, Darmstadt, Germany; Novartis; Roche; Teva; and Sanofi and research funding from Allmiral; Biogen; the healthcare business of Merck KGaA, Darmstadt, Germany; Hexal; Novartis; Roche; Sanofi; Teva; and Viatris. M.K. Houtchens has received research support from Genentech and Biogen. M. Magyari has served on scientific advisory boards for Sanofi, Novartis, Moderna, and the healthcare business of Merck KGaA, Darmstadt, Germany, and has received honoraria for lecturing from Biogen; the healthcare business of Merck KGaA, Darmstadt, Germany; Novartis; Roche; Sanofi; and Bristol Myers Squibb. G. Merki-Feld has received personal compensation as a speaker/consultant from Novartis, Teva, Gedeon Richter, HRA Pharma, Lundbeck, and the healthcare business of Merck KGaA, Darmstadt, Germany. S. Montgomery has received research support from Roche, Novartis, and AstraZeneca and speaker's honorarium from Teva, as well as served on a study advisory board for IQVIA. R.E. Nappi has past financial relationships (lecturer, member of advisory boards, and/or consultant) with Boehringer Ingelheim, Eli Lilly, Endoceutics, Gedeon Richter, HRA Pharma, Merck Sharpe & Co. (Kenilworth, NJ), Organon & Co., Palatin Technologies, Pfizer Inc., Procter & Gamble Co., TEVA Women's Health Inc., and Zambon SpA. At present, she has ongoing relationships with Abbott; Astellas; Bayer HealthCare AG; Besins Healthcare; Exeltis; Fidia; the healthcare business of Merck KGaA, Darmstadt, Germany; Novo Nordisk; Shionogi Limited; Theramex; Viatris; and Vichy Laboratories. W. Shen has received research support from the NIH; Astellas; the healthcare business of Merck KGaA, Darmstadt, Germany; Bayer and Pfizer. E. Stenager has no disclosures apart from the funding of this project. H. Thompson has received honoraria and travel grants from the healthcare business of Merck KGaA, Darmstadt, Germany; Biogen; and Novartis. Z. Tulek has no conflicts of interest to declare. K. Marhardt is an employee of Merck GmbH, Vienna, Austria, an affiliate of Merck KGaA, Darmstadt, Germany. J.A. Hillert has received honoraria for serving on advisory boards for Biogen; Bristol Myers Squibb/Celgene; Janssen; the healthcare business of Merck KGaA, Darmstadt, Germany; Sandoz; and Sanofi and speaker's fees from Biogen; Janssen; Novartis; the healthcare business of Merck KGaA, Darmstadt, Germany; Teva; Sandoz; and Sanofi. He has served as principal investigator for projects sponsored by, or received unrestricted research support from, Biogen; Bristol Myers Squibb/Celgene; Janssen; the healthcare business of Merck KGaA, Darmstadt, Germany; Novartis; Roche; and Sanofi. His MS research is funded by the Swedish Brain Foundation. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Publication History

Received by *Neurology® Clinical Practice* March 7, 2025. Accepted in final form December 4, 2025. Submitted and externally peer-reviewed. The handling editor was Deputy Editor Kathryn Kvam, MD.

References

1. Jakimovski D, Bittner S, Zivadinov R, et al. Multiple sclerosis. *Lancet.* 2024;403(10422):183-202. doi:10.1016/S0140-6736(23)01473-3
2. Freeman L, Lucas A, Zhou J, Hayward B, Gough M, Livingston T. Outcomes and health care service use in adults 50 years or older with and without multiple sclerosis: a 6-year observational analysis. *Int J MS Care.* 2023;25(2):56-62. doi:10.7224/1537-2073.2021-124
3. Omar ES, Suliman HM, Osman B, Abdalla SA, Abdoon IH. Disease-modifying therapies as positive predictors of quality of life for Sudanese patients with multiple sclerosis: a cross-sectional study. *Egypt J Neurol Psychiatry Neurosurg.* 2024;60(1):77. doi:10.1186/s41983-024-00855-3
4. Bove R, Okai A, Houtchens M, et al. Effects of menopause in women with multiple sclerosis: an evidence-based review. *Front Neurol.* 2021;12:554375. doi:10.3389/fneur.2021.554375
5. Bove R, Vaughan T, Chitnis T, Wicks P, De Jager PL. Women's experiences of menopause in an online MS cohort: a case series. *Mult Scler Relat Disord.* 2016;9:56-59. doi:10.1016/j.msard.2016.06.015
6. Murgia F, Giagnoni F, Lorefice L, et al. Sex hormones as key modulators of the immune response in multiple sclerosis: a review. *Biomedicines.* 2022;10(12):3107. doi:10.3390/biomedicines10123107
7. Ysrraelit MC, Correale J. Impact of andropause on multiple sclerosis. *Front Neurol.* 2021;12:766308. doi:10.3389/fneur.2021.766308
8. NICE. *Multiple Sclerosis: How Common Is It?* Accessed October 3, 2024. cks.nice.org.uk/topics/multiple-sclerosis/background-information/prevalence/
9. Thakolwiboon S, Mills EA, Yang J, et al. Immunosenescence and multiple sclerosis: inflammaging for prognosis and therapeutic consideration. *Frontiers in aging.* 2023;4.1234572. 10.3389/fragi.2023.1234572
10. Kaisey M, Sicotte N, Giesser B. Multiple sclerosis management and reproductive changes: a guide for general neurologists. *Neurol Clin Pract.* 2018;8(2):142-147. doi:10.1212/CPJ.0000000000000436
11. Ysrraelit MC, Correale J. Impact of sex hormones on immune function and multiple sclerosis development. *Immunology.* 2019;156(1):9-22. doi:10.1111/imm.13004
12. Blümel JE, Lavín P, Vallejo MS, Sarrá S. Menopause or climacteric, just a semantic discussion or has it clinical implications? *Climacteric.* 2014;17(3):235-241. doi:10.3109/13697137.2013.838948
13. World Health Organization. Menopause. Accessed June 1, 2024. who.int/news-room/fact-sheets/detail/menopause
14. Cleveland Clinic. Postmenopause: Signs, *Symptoms & What to Expect.* Accessed June 1, 2024. my.clevelandclinic.org/health/diseases/21837-postmenopause
15. The North American Menopause Society. *Menopause 101: A primer for the perimenopausal.* Accessed December 10, 2023. https://www.atimeofmyown.com/uploads/5/1/1/6/51161337/menopause_101__a_primer_for_the_perimenopausal.pdf
16. Brancati S, Gozzo L, Longo L, Vitale DC, Drago F. Rituximab in multiple sclerosis: are we ready for regulatory approval? *Front Immunol.* 2021;12:661882. doi:10.3389/fimmu.2021.661882
17. Lorefice L, D'Alterio MN, Firinu D, Fenu G, Cocco E. Impact of menopause in patients with multiple sclerosis: current perspectives. *Int J Womens Health.* 2023;15:103-109. doi:10.2147/IJWH.S334719
18. Salonia A. EAU *Guidelines on Sexual and Reproductive Health–Uroweb*. Accessed July 13, 2025. https://uroweb.org/guidelines/sexual-and-reproductive-health/chapter/male-hypogonadism
19. Bassil N. Late-onset hypogonadism. *Med Clin North Am.* 2011;95(3):507-523. doi:10.1016/j.mcna.2011.03.001

Downloaded from https://www.neurology.org by 78.134.103.86 on 30 October 2026

20. Nieschlag E. Late-onset hypogonadism: a concept comes of age. *Andrology.* 2020; 8(6):1506-1511. doi:10.1111/andr.12719
21. Dudek P, Kozakowski J, Zgliczyński W. Late-onset hypogonadism. *Prz Menopauzalny.* 2017;16(2):66-69. doi:10.5114/pm.2017.68595
22. Bove R, Musallam A, Healy BC, et al. Low testosterone is associated with disability in men with multiple sclerosis. *Mult Scler.* 2014;20(12):1584-1592. doi:10.1177/1352458514527864
23. Balshem H, Helfand M, Schünemann H, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* 2011;64(4):401-406. doi:10.1016/j.jclinepi.2010.07.015
24. Bove R, Chitnis T, Houtchens M. Menopause in multiple sclerosis: therapeutic considerations. *J Neurol.* 2014;261(7):1257-1268. doi:10.1007/s00415-013-7131-8
25. Midaglia L, Otero S, Baró F, Montalban X, Tintoré M. Menopause and multiple sclerosis: influence on prognosis and role of disease-modifying drugs and hormonal replacement therapy. *Mult Scler.* 2022;28(2):173-182. doi:10.1177/1352458520952022
26. The 2022 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(7):767-794. doi:10.1097/GME.0000000000002028
27. Ladeira F, Salavisa M, Caetano A, Barbosa R, Sá F, Correia AS. The influence of menopause in multiple sclerosis course: a longitudinal cohort study. *Eur Neurol.* 2018; 80(3-4):223-227. doi:10.1159/000496374
28. Bove R, Anderson A, Rowles W, Rankin KA, Hills MG. A hormonal therapy for menopausal women with MS: a phase Ib/IIa randomized controlled trial - multiple sclerosis and related disorders. *Mult Scler Relat Disord.* 2022;61:1037-1047.
29. Geraci A, Calvani R, Ferri E, Marzetti E, Arosio B, Cesari M. Sarcopenia and menopause: the role of estradiol. *Front Endocrinol.* 2021;12:682012. doi:10.3389/fendo.2021.682012
30. Singh J, Anderson A, Rowles W, et al. MS DREAMS: menopause and sleep dysfunction: reports and assessments from multiple sclerosis patients. *Mult Scler.* 2021; 27:134-740 [Abstract P166].
31. Todd A, Stuifbergen A. Barriers and facilitators related to breast cancer screening. *Int J MS Care.* 2011;13(2):49-56. doi:10.7224/1537-2073-13.2.49
32. Otero-Romero S, Midaglia L, Carbonell-Mirabent P, et al. Menopause does not modify disability trajectories in a longitudinal cohort of women with clinically isolated syndrome and multiple sclerosis followed from disease onset. *Eur J Neurol.* 2022; 29(4):1075-1081. doi:10.1111/ene.14782
33. Kamińska MS, Schneider-Matyka D, Rachubińska K, Panczyk M, Grochans E, Cybulska AM. Menopause predisposes women to increased risk of cardiovascular disease. *J Clin Med.* 2023;12(22):7058. doi:10.3390/jcm12227058
34. Baillargeon J, Al Snih S, Raji MA, et al. Hypogonadism and the risk of rheumatic autoimmune disease. *Clin Rheumatol.* 2016;35(12):2983-2987. doi:10.1007/s10067-016-3330-x
35. Cai M, Cui R, Yang P, et al. Incidence and risk factors of hypogonadism in male patients with latent autoimmune diabetes and classic type 2 diabetes. *Front Endocrinol (Lausanne).* 2021;12:675525. doi:10.3389/fendo.2021.675525
36. Türk Börü Ü, Köseoğlu Toksoy C, Bölük C, Bilgiç A, Taşdemir M. Effects of multiple sclerosis and medications on menopausal age. *J Int Med Res* 2018;46(3):1249-1253. doi:10.1177/0300060517746026
37. Zeydan B, Kantarci OH. Impact of age on multiple sclerosis disease activity and progression. *Curr Neurol Neurosci Rep.* 2020;20(7):24. doi:10.1007/s11910-020-01046-2
38. Zeydan B, Atkinson EJ, Weis DM, et al. Reproductive history and progressive multiple sclerosis risk in women. *Brain Commun.* 2020;2:fcaa185. doi:10.1093/braincomms/fcaa185
39. Cocco E, Sardu C, Gallo P, et al. Frequency and risk factors of mitoxantrone-induced amenorrhea in multiple sclerosis: the FEMIMS study. *Mult Scler.* 2008;14(9): 1225-1233. doi:10.1177/1352458508094882
40. EMC. *Cyclophosphamide Tablets 50 Mg - Summary of Product Characteristics.* 2016. Accessed November 22, 2023. medicines.org.uk/emc/product/1813/smpc/print
41. Harlow SD, Gass M, Hall JE, et al. Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging. *Menopause.* 2012;19(4):387-395. doi:10.1097/gme.0b013e31824d8f40
42. Oreja-Guevara C, Lopez-Coello S, Rodriguez-Rabanal R, Gómez-Estevez J, Díaz-Díaz J. Menopause in multiple sclerosis. *Mult Scler J* 2020;26:118-659.
43. Saoji VA. Premature ovarian failure due to cyclophosphamide: a report of four cases in dermatology practice. *Indian J Dermatol Venereol Leprol.* 2008;74(2):128-132. doi: 10.4103/0378-6323.39696
44. Bove R, Healy BC, Secor E, et al. Patients report worse MS symptoms after menopause: findings from an online cohort. *Mult Scler Relat Disord.* 2015;4(1):18-24. doi: 10.1016/j.msard.2014.11.009
45. Bove R, Healy BC, Musallam A, Glanz BI, De Jager PL, Chitnis T. Exploration of changes in disability after menopause in a longitudinal multiple sclerosis cohort. *Mult Scler.* 2016;22(7):935-943. doi:10.1177/1352458515606211
46. Sparaco M, Bonavita S. The role of sex hormones in women with multiple sclerosis: from puberty to assisted reproductive techniques. *Front Neuroendocrinol.* 2021;60: 100889. doi:10.1016/j.yfrne.2020.100889
47. Baroncini D, Annovazzi PO, De Rossi N, et al. Impact of natural menopause on multiple sclerosis: a multicentre study. *J Neurol Neurosurg Psychiatry.* 2019;90(11): 1201-1206. doi:10.1136/jnnp-2019-320587
48. Bove R. Menopause may worsen the symptoms of multiple sclerosis. *Mult Scler.* 2013; 19:31.
49. Baroncini D. What is the impact of natural menopause on multiple sclerosis? An Italian, multicentre, retrospective, observational study. *Mult Scler.* 2018;24: 147-148.
50. Freedman MS, Devonshire V, Duquette P, et al. Treatment optimization in multiple sclerosis: canadian MS working group recommendations. *Can J Neurol Sci.* 2020; 47(4):437-455. doi:10.1017/cjn.2020.66

eReferences available as Supplementary Material at Neurology.org/cp

How to cite this article: Bove R, Simoni M, Castelo-Branco C, et al. Expert opinion on age-related sex hormone changes and hypogonadism in people with multiple sclerosis: a Delphi consensus program. *Neurol Clin Pract.* 2026;16(2):e200588. doi: 10.1212/CPJ.0000000000200588

Downloaded from https://www.neurology.org by 78.134.103.86 on 30 October 2026