VOLUME 90 • NUMBER 4 • APRIL 2023 • www.ccjm.org

CME MOC

Cleveland Clinic Journal of Medicine

Centralized pain syndromes: A rheumatologist's perspective

Brodie abscess in an 87-year-old

Ascites, bacterial peritonitis, and hepatorenal syndrome: Diagnosis and management

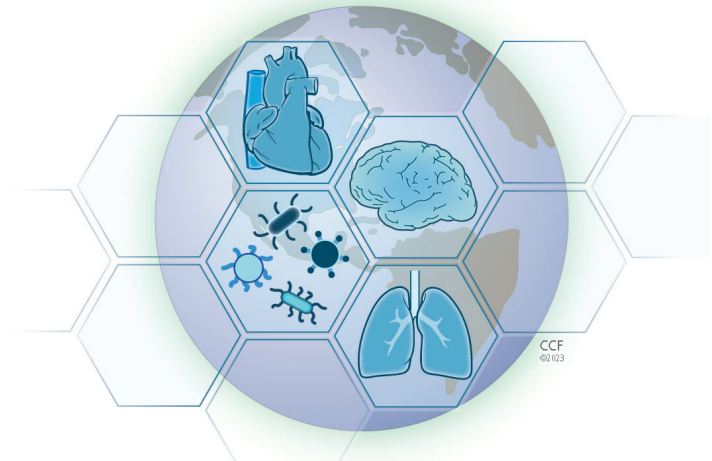
Heart failure with reduced ejection fraction: A guideline review

Paternalism in practice: How we create obstacles for sexual, reproductive, and menopausal healthcare despite our best intentions

Reproductive issues and multiple sclerosis: 20 questions

Central sensitization, chronic pain, and other symptoms: Improving understanding and management

How does climate change impact our patients?



CLEVELAND CLINIC JOURNAL OF MEDICINE

ADVERTISING
Sima Sherman, Director of Sales and Marketing
SHERMAN MEDICAL MARKETING GROUP
1628 John F. Kennedy Blvd., #2200, Philadelphia, PA 19103
(610) 529-0322 • sima@shermanmmg.com

SUBSCRIPTIONS
U.S. and possessions: Personal $160; institutional $188; single copy/back issue $20

Foreign: $205; single copy/back issue $20

Institutional (multiple-reader rate) applies to libraries, schools, hospitals, and federal, commercial, and private institutions and organizations. Individual subscriptions must be in the names of, billed to, and paid by individuals.

Please make check payable to *Cleveland Clinic Journal of Medicine* and mail to: Cleveland Clinic Education Foundation, P.O. Box 373291, Cleveland, OH 44193-3291. To purchase a subscription with a credit card, please visit www.ccjm.org.

REPRINTS
(610) 529-0322 • sima@shermanmmg.com

PHOTOCOPYING
Authorization to photocopy items for internal or personal use is granted by *Cleveland Clinic Journal of Medicine* (ISSN 0891-1150 [print], ISSN 1939-2869 [online]), published by Cleveland Clinic, provided that the appropriate fee is paid directly to Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923 USA (978) 750-8400. Prior to photocopying items for educational classroom use, please contact Copyright Clearance Center, Inc., at the address above. For permission to reprint material, please fax your request with complete information to the Republication department at CCC, fax (978) 750-4470. For further information visit CCC online at www.copyright.com. To order bulk reprints, see above.

CHANGE OF ADDRESS
To report a change of address, send a recent mailing label along with new information to:

AMA, Data Verification Unit, 330 N. Wabash Ave., Suite 39300, Chicago, IL 60611-5885 • Phone (800) 621-8335 • Fax (312) 464-4880 • dpprodjira@ama-assn.org

Cleveland Clinic Journal of Medicine uses the AMA database of physician names and addresses. The database includes all US physicians and not just AMA members. Only the AMA can update changes of address and other data.

SUBSCRIPTIONS, EDITORIAL, BILLING, AND PRODUCTION
9500 Euclid Avenue, JJ44, Cleveland, OH 44195 • Phone (216) 444-2661 • Fax (216) 444-9385 • ccjm@ccf.org • www.ccjm.org

Cleveland Clinic Journal of Medicine [ISSN 0891-1150 (print), ISSN 1939-2869 (online)] is published monthly by Cleveland Clinic at 9500 Euclid Avenue, JJ44, Cleveland, OH 44195.

2023

APRIL

IBD MASTER CLASS: THE CLEVELAND CLINIC MEDICAL AND SURGICAL TEAM APPROACH TO COMPLEX IBD
April 3–4
Live stream

HEALTHCARE DELIVERY AND IMPLEMENTATION SCIENCE CENTER SPEAKER SERIES
April 11
Virtual

SOUTHWESTERN CONFERENCE ON MEDICINE
April 13–16
Tucson, AZ

EASE YOUR WAY INTO THE ESOPHAGUS
April 14
Cleveland, OH

MAY

BIOLOGIC THERAPIES SUMMIT X AND VASCULITIS 2023
May 11–13
Cleveland, OH

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: COACH APPROACH TO THE ANNUAL PROFESSIONAL REVIEW
May 17–18
Live stream

DIABETES DAY
May 18
Cleveland, OH, and live stream

THE PRESENT AND FUTURE OF EP PRACTICE 2023: THE CLEVELAND CLINIC PERSPECTIVE
May 18
New Orleans, LA

UVEITIS UPDATE
May 20
Cleveland, OH

JUNE

INNOVATIONS IN CEREBROVASCULAR CARE
June 8–9
Cleveland, OH

INTENSIVE REVIEW OF INTERNAL MEDICINE
June 12–16
Live stream

INTERNAL MEDICINE UPDATES AND BOARD REVIEW: CERTIFICATION, RECERTIFICATION, AND MOC PREPARATION
June 19–23
Weston, FL

MELLEN CENTER UPDATE IN MULTIPLE SCLEROSIS (MS)
June 23
Cleveland, OH

JULY

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: COACHING AND MENTORING ESSENTIALS FOR HEALTHCARE PROFESSIONALS
July 12
Live stream

CLEVELAND SPINE REVIEW: HANDS-ON 2023
July 19–24
Cleveland, OH

AUGUST

NEUROLOGY UPDATE: A COMPREHENSIVE REVIEW FOR THE CLINICIAN
August 11–13
Washington, DC

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) SPECIALIST COURSE
August 23–25
Cleveland, OH

PEDIATRIC BOARD REVIEW
August 27–September 1
Cleveland, OH

SEPTEMBER

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: HEALTHCARE PROFESSIONALS COACH TRAINING
September 6–7
Live stream

HOSPITAL MEDICINE 2023
September 7–8
Cleveland, OH

INNOVATIONS IN NEUROSCIENCE
September 8
Cleveland, OH

OBESITY SUMMIT
September 21–22
Cleveland, OH, and live stream

PRACTICAL MANAGEMENT OF STROKE
September 22
Warrensville Heights, OH

COMPREHENSIVE, LIFELONG, EXPEDITIOUS (CLE) CARE OF AORTIC DISEASE
September 22–23
Cleveland, OH

WAKE UP TO SLEEP DISORDERS 2023: A CLEVELAND CLINIC SLEEP DISORDERS CENTER UPDATE
September 22–24
Cleveland, OH

OHIO OCULAR ONCOLOGY SYMPOSIUM
September 23–24
Beachwood, OH

GLOBAL EP
September 29–30
Cleveland, OH

MIDWEST GLAUCOMA SYMPOSIUM
September 30
Cleveland, OH

OCTOBER

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: COACHING AND MENTORING ESSENTIALS FOR HEALTHCARE PROFESSIONALS
October 11–12
Live stream

INTENSIVE REVIEW OF ENDOCRINOLOGY AND METABOLISM
October 13–15
Cleveland, OH

CV UPDATE FOR THE PRIMARY CARE PROVIDER: IMPROVING CV CARE ACCESS AND OUTCOMES ACROSS ALL COMMUNITIES
October 19–20
Cleveland, OH

RESTORING NEUROLOGICAL FUNCTION: THE CROSSROADS OF NEUROLOGY, PSYCHIATRY, AND NEUROSURGERY
October 27
Cleveland, OH

UTILIZING ARTIFICIAL INTELLIGENCE IN THE PREVENTION AND MANAGEMENT OF CARDIOVASCULAR DISEASE: APPLICATIONS, BENEFITS, AND CHALLENGES
October 27–28
Chicago, IL

FOR SCHEDULE UPDATES AND TO REGISTER, VISIT: WWW.CCFCME.ORG/LIVE

Table of Contents

CONTINUED ON PAGE 199

Upcoming Features

- Management of trigeminal neuralgia: Guidelines from the Royal College of Surgeons
- Fractional exhaled nitric oxide in the diagnosis and management of asthma

CONTINUED FROM PAGE 195

Cleveland Clinic

Attend In Person or Live Stream

27th Annual

Diabetes Day

Therapeutics, Technology and Surgery

Wednesday, May 18, 2023

InterContinental Hotel and Conference Center | Cleveland, OH and Live Stream

Register Today! **ccfcme.org/diabetesday23**

This course will provide up-to-date reviews of management strategies and research on the complications of diabetes. Key topic areas that will be addressed include:

- A review of therapeutic options to manage both Type 1 and 2 diabetes and their complications, including a pump update, novel insulin delivery systems, and new insulins continuous glucose monitoring updates.
- Treatment of hypoglycemia and diabetic cardiomyopathy.
- Importance of obesity medical management vs. surgical management.
- New hypertension and lipid guidelines.
- New roles for GLP1 receptor agonists and SGLT-2 inhibitors and mineralocorticoid receptor antagonists in preserving renal function and cardiac function.
- The role of dietary carbs in diabetes and pregnancy.

This year's curriculum will also feature discussions about:

- New insulins that may avoid hypoglycemia.
- New treatment for retinopathy.
- New therapies to prevent Type 1 diabetes.
- Diabetes and elderly populations.
- Pancreas and islet transplant and oral agent therapy in the hospital.
- New therapies for diabetic neuropathy.

The goal of this symposium is to increase practitioners' competence and clinical performance to treat diabetes and its complications and, ultimately, to improve patient outcomes.

New this year is an optional workshop on continuous glucose monitoring designed for health care providers to advance the care of their patients with diabetes on the use of continuous glucose monitoring and other diabetes technology.

Join your colleagues in person or participate virtually from the convenience of your home or office

This activity has been approved for *AMA PRA Category 1 Credits*™, ANCC Contact Hours and AAPA Category 1 CME Credits.

Chronic centralized pain syndromes: A rheumatologist's perspective

Chronic centralized pain syndromes are extremely important, common, and vexing for both patients and clinicians. In this issue of the *Journal*, Volcheck et al[1] present a framework that I believe is useful for understanding chronic centralized pain and for developing an actionable treatment plan for patients.

It has been estimated that more than 30% of primary care visits relate to the need to address painful conditions. I would guess that a significant number of those patients have chronic generalized pain not explained by a specific injury or demonstrable inflammation, and that they are ultimately diagnosed with fibromyalgia, the prototypic central sensitization pain syndrome. While there are regional and individual physician differences in practice behavior, many of these patients are referred to rheumatologists despite the absence of a clinically demonstrated and relevant inflammatory or autoimmune pathobiology.

For decades there have been discussions within the rheumatologic community, including live debate at our annual rheumatology scientific meeting, whether such referral is appropriate or ultimately of net benefit. I would characterize this debate as ongoing and overlapping with similar debate regarding referral of patients with chronic fatigue syndrome (myalgic encephalomyelitis) and now with "long COVID." Given the high prevalence of these syndromes and the limited number of rheumatologists, many rheumatology practices have declined to accept for consultation or provide ongoing chronic care for patients with these diagnoses. Our clinic has not made it a rule to do that, which has translated into some days scheduled with at least half of my patients experiencing fibromyalgia or a related syndrome as their primary concern, with the current buzzword for referral being "suspected autoimmune disease." As a result, I frequently struggle to fit patients with joint or urgent organ-threatening inflammatory issues into my schedule in a timely manner.

In writing the above, I do not wish to minimize in any way the significant impact of chronic pain and fatigue on the lives of patients with fibromyalgia and related disorders. As Volcheck et al discuss in this issue of the *Journal*, patient and physician education are essential in the management of patients with chronic centralized pain. I believe that too often there is a lack of understanding and acceptance of the concepts of central sensitization. Often, there is a lack of comfort in making and accepting the diagnosis. The patient is questioning how they can have so much pain and if this is all in their head, and the clinician is examining what they are missing, and how to be sure that this is not an autoimmune disorder heralded by pain and fatigue. It is this last concern that leads to the ordering of a panoply of serologic immunologic tests, especially antinuclear antibody (ANA), despite the absence of any clinical or laboratory features truly suggestive of lupus or related conditions. Several studies indicate the strikingly limited (virtually zero) utility of checking ANA in patients with symptoms limited to generalized pain and fatigue,[2] especially when careful examination of skin, lymph nodes, muscle strength, and joints and a complete blood count, comprehensive metabolic panel, and thyroid-stimulating hormone are unrevealing. Yet the practice of ANA testing remains prevalent. If results are weakly positive, which may be present in about 25% of the healthy population,[2] patients are diagnosed with an autoimmune disorder and are referred

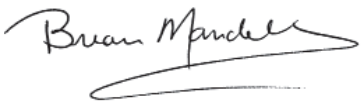
doi:10.3949/ccjm.90b.04023

to specialists for evaluation, a practice almost guaranteed to increase patient stress and their expectation for pharmacotherapy.

Despite several direct-to-consumer advertising campaigns, the benefits of pharmacotherapy for patients with fibromyalgia and central sensitization syndromes are modest at best. There are benefits for treating patients with coexistent significant anxiety, depression, bipolar disorders, or specific sleep disorders, and patients should be evaluated for these conditions. But patients can usually be directly diagnosed with fibromyalgia, with or without these associated conditions.[3] Fibromyalgia is not just a "wastebasket" diagnosis of exclusion or frustration.

While it is always important to keep an open mind and avoid the clinical sin of premature closure, making the diagnosis with confidence is important. Reassurance and behavioral treatment approaches can be provided,[1,3] and previous patient experiences and symptoms can be explained and even described by the clinician without hearing them from the patient. For example, on "less-bad" days, patients try to accomplish many tasks that they could not do the preceding few days and then end up almost disabled by pain or fatigue for the next several days, by the development of intolerance to touch, strong odors, or noises, by dyspareunia (in women), and by the sensation of pain from frequent culture-negative urinary tract infections (interstitial cystitis). Recognition of these chronic central pain syndromes is also important when addressing other comorbidities, as the presence of significant fibromyalgia may reduce the perceived benefits following joint replacement or spine surgery.

While I have significant reservations about the current "narcotics for no one" approach to pain management (speaking from personal experience after undergoing surgically treated renal colic), opioids should be avidly avoided in the treatment of fibromyalgia and related central pain syndromes.



Brian F. Mandell, MD, PhD
Editor in Chief

1. **Volcheck MM, Graham SM, Fleming KC, Mohabbat AB, Luedtke CA.** Central sensitization, chronic pain, and other symptoms: better understanding, better management. Cleve Clin J Med 2023; 90(4):245–254. doi:10.3949/ccjm.90a.22019
2. **Nashi RA, Shmerling RH.** Antinuclear antibody testing for the diagnosis of systemic lupus erythematosus. Med Clin N Am 2021; 105(2):387–396 doi:10.1016/j.mcna.2020.10.003
3. **Gota CE.** Fibromyalgia: recognition and management in the primary care office. Rheum Dis Clin N Am 2022; 48(2):467–478. doi:10.1016/j.rdc.2022.02.006

Cleveland Clinic

Ultrasound Workshop: Diagnostic and Procedural Skills

Focus on the Hospitalized Patient

May 10-13, 2023

Cleveland Clinic Simulation and Advanced Skills Center
Cleveland, OH

Hemodynamic Assessment of the Critically Ill Patient Saturday, May 13

You'll Want To Be At This Workshop

The use of ultrasound to diagnose and guide procedures is growing rapidly and you don't want to be left behind. This growth is primarily fueled by data indicating that ultrasound can improve the success rate of various procedures while decreasing complications. This ultrasound workshop will provide you with current state-of-the-art techniques for diagnosis and guiding procedures. You will be able to incorporate the lessons you learn by attending this workshop into your clinical practice.

Stay Current With These Objectives

Wednesday Optional Workshop	2-Day Course	Saturday Optional Workshops
• Building a Point-of-Care Ultrasound Program • Describe the components of successful point-of-care ultrasound programs • Summarize process for image acquisition, machine utilization, and IT configuration • Describe the importance of a training, quality improvement, and credentialing • List components of billing and coding for various ultrasound exams	• Summarize the basic science and diagnostic use of ultrasound imaging • Describe the protocols, evaluation, and best use of echocardiography in critically ill patients • Review the role of ultrasound in a focused assessment with sonography in trauma (FAST) exam to assess for free fluid in the abdomen or around the heart • Summarize the basics of using ultrasound to assess lungs • Describe the most effective diagnostic use of ultrasound to assess for vascular abnormalities including aortic pathology and deep venous thrombosis • Practice the evaluation of shock and respiratory failure with point-of-care echocardiography • Demonstrate competence in ultrasound guidance for needle placement and peripheral intravenous access, arterial line access, and midline access • Demonstrate the best use of ultrasound for paracentesis, thoracentesis, and arthrocentesis • Describe the fundamentals of tunneling technique and the tunneled CVC kit • List the indications, complications, and aftercare related to insertion of a tunneled central venous catheter (CVC) • Demonstrate competence in central venous access including materials, ultrasound landmarks, and needle placement	**Airway Management in the Critically Ill Patient** • Summarize the Cleveland Clinic Airway Management protocol and algorithm for critically ill patients • Apply airway management tools to secure the airway • Demonstrate application of the airway management protocol • Choose the best strategy to manage the airway in critically ill patients **Pediatric Simulations and Ultrasound** • Detail the causes of hypoxemia in the critically ill neonate • Effectively manage undifferentiated shock in the neonate and infant • Describe tips and tricks for vascular access in the pediatric population **Hemodynamic Assessment of the Critically Ill Patient** • Identify the hemodynamically compromised patient • Describe the 3 components of the Rapid Ultrasound for Shock and Hypotension (RUSH) exam: Pump, Tank, Pipes • Utilize the Rapid Ultrasound for Shock and Hypotension (RUSH) exam protocol • Explain the ultrasound findings seen in the 4 types of distributive shock

Who Should Attend

This workshop is designed for physicians, physician assistants, and nurse practitioners in emergency medicine, internal medicine, hospital medicine, critical care, cardiology, general surgery, pediatrics, pulmonology, anesthesiology, and radiology.

Register Today! ccfcme.org/GoUltra

This activity is approved for *AMA PRA Category 1 Credit™*, ANCC Contact Hours, and AAPA Category 1 CME Credits.

Masumi Suzuki Shimizu, MD
Assistant Professor, Department of Infectious Diseases, Nagasaki University Hospital, Nagasaki, Japan

Kohsuke Matsui, MD
Assistant Professor, Department of Infectious Diseases, Nagasaki University Hospital, Nagasaki, Japan

Brodie abscess in an 87-year-old man

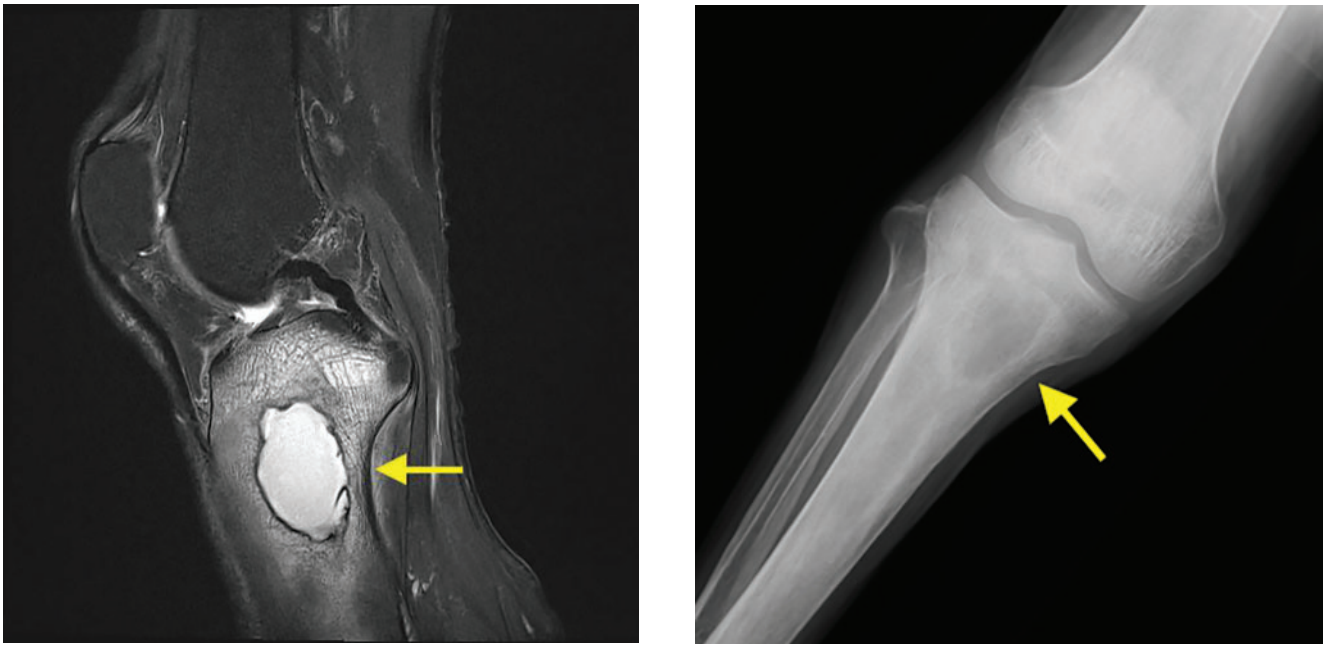


Figure 1. Imaging results of the patient's lower right leg taken 1 year before hospital admission. On the left, T2-weighted magnetic resonance imaging shows an encapsulated abscess surrounded by granulation tissue and bone edema (arrow) in the proximal part of the right tibia, causing subacute osteomyelitis. On the right, radiography shows a mass lesion (arrow), misdiagnosed as a bone tumor.

An 87-year-old man presented to an orthopedic clinic with a 2-month history of dull pain below his right knee. Magnetic resonance imaging revealed an encapsulated mass in the right tibia (**Figure 1**). Based on this result and the patient's clinical course, subacute osteomyelitis was suspected, but the patient was managed symptomatically without antibiotic treatment because his symptoms and general condition were mild and stable.

One year later, he was admitted to the hospital because of swelling of the anterior aspect of the right proximal tibia. At that time, he was afebrile, without any history of a possible source of infection such as recent trauma or dental procedure.

Laboratory testing results revealed elevation of the following inflammatory markers:

- White blood cell count 9.3 × 10^3 cells/μL (reference range 3.3–8.6)
- C-reactive protein level 65.2 mg/L (0–3)
- Erythrocyte sedimentation rate 100 mm/h (2–10).

Computed tomography and plain radiography revealed a sinus tract connecting the tibial lesion to the subcutaneous tissue (**Figure 2**). The patient underwent surgical debridement of the abscess. Culture of a pus sample obtained intraoperatively grew methicillin-resistant *Staphylococcus aureus*, but a blood culture

doi:10.3949/ccjm.90a.22041

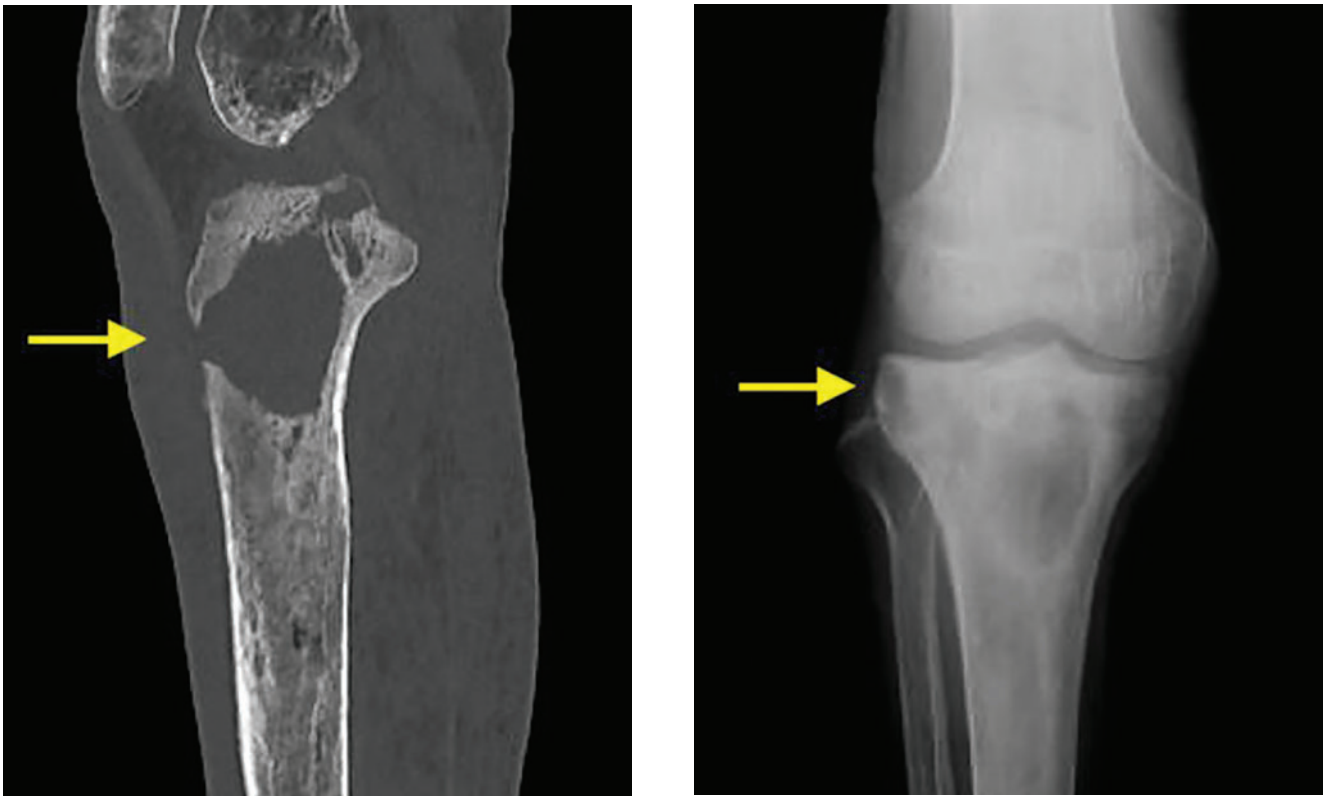


Figure 2. On hospital admission, computed tomography (left) demonstrated a well-visualized sinus tract connecting to subcutaneous tissue (arrow), and radiography (right) of the abscess showed well-circumscribed osteolysis with sclerotic margins (arrow), which had developed during the year since the initial presentation.

was negative. According to the patient's clinical course and imaging findings, he was suspected of having presented with Brodie abscess at his initial presentation at the orthopedic clinic 1 year earlier, and the lesion was considered to represent a deterioration of untreated chronic osteomyelitis since that time.

The patient's symptoms improved with a 4-week course of intravenous vancomycin. He continued antibiotic therapy after discharge, with a 3-month course of oral minocycline. At a follow-up visit 6 months after debridement, his symptoms were controlled with no evidence of clinical relapse.

BRODIE ABSCESS: CAUSES AND CLINICAL COURSE

Brodie abscess, first reported in 1832 by Sir Benjamin Collins Brodie,[1] is a rare form of subacute or chronic osteomyelitis, usually affecting the metaphysis of long bone. Most cases occur in children and young adults, and the most commonly affected bone is the tibia.[2–5] *S aureus* is the most common causative pathogen (over 60% of cases), followed by gram-negative rods, including *Enterobacteriaceae* and *Pseudomonas aeruginosa*, although 20% of cases are culture-negative.[2,3] These pathogens are also the most common cause of acute infections, including osteomyelitis.[6] However, patients with Brodie abscess can present with an insidious course, with or without fever,[7–9] potentially leading to misdiagnosis of a benign or malignant bone tumor and delay in appropriate antibiotic treatment. The main source of infection is by hematogenous spread, which is often unclear because of the long clinical course of the disease.

A systematic review revealed that the possible etiologies were reported only in 56 of 407 cases, with both recent systemic infection and minor trauma being present.[3] The diagnosis of Brodie abscess is confirmed based on results of radiologic imaging and culture. Inflammatory markers are unreliable diagnostic tools for Brodie abscess as they frequently show only a slight elevation or are within the normal range.[3] In our patient, the C-reactive protein level was mildly elevated, but the erythrocyte sedimentation rate was significantly elevated.

TREATMENT IS SURGICAL AND MEDICAL

The standard treatment for Brodie abscess is a combination of surgical debridement and systemic antibiotic therapy.[3] If the culture results reveal the causative pathogens, these results should guide the choice of antibiotic.

Antibiotic treatment duration varies from at least 10 days to 3 months or longer, depending on the clinical condition of the patient. However, patients are often treated for 4 to 6 weeks, including a few weeks of intravenous antibiotics combined with surgical debridement.[3,7] Regarding surgical intervention, large cavities sometimes require stabilization by bone grafting.[2] Although data on outcomes are limited, relapse rates are reported to be approximately 15% for Brodie abscess[3] and 20% for chronic osteomyelitis.[10]

Our 87-year-old patient was observed symptomatically by his primary physician for 1 year with slow progression of his disease, which characterized the typical chronic clinical course of this disease. However, the treatment should be initiated as soon as possible when a chronic abscess is suspected, as case reports also reveal that delay of treatment can slowly exacerbate the abscess, eventually leading to a sinus tract, a fistula connecting skin and soft tissue, or bone fracture.[3,9,11]

Brodie abscess is rare in older adults. However, timely diagnosis and treatment can prevent exacerbation of the abscess and avoid the need for additional surgical treatment such as bone grafting or amputation, thus shortening the duration of hospitalization and preventing long-term complications.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Brodie BC.** An account of some cases of chronic abscess of the tibia. Med Chir Trans 1832; 17:239–249. doi:10.1177/095952873201700111
2. **Olasinde AA, Oluwadiya KS, Adegbehingbe OO.** Treatment of Brodie's abscess: excellent results from curettage, bone grafting, and antibiotics. Singapore Med J 2011; 52(6):436–439. pmid:21731997
3. **van der Naald N, Smeeing DPJ, Houwert RM, Hietbrink F, Govaert GAM, van der Velde D.** Brodie's abscess: a systematic review of reported cases. J Bone Jt Infect 2019; 4(1):33–39. doi:10.7150/jbji.31843
4. **Qi R, Colmegna I.** Brodie abscess. CMAJ 2017; 189(3):E117. doi:10.1503/cmaj.151419
5. **Nolla JM, Ariza J, Gómez-Vaquero C, et al.** Spontaneous pyogenic vertebral osteomyelitis in nondrug users. Semin Arthritis Rheum 2002; 31(4):271–278. doi:10.1053/sarh.2002.29492
6. **Dartnell J, Ramachandran M, Katchburian M.** Haematogenous acute and subacute paediatric osteomyelitis: a systematic review of the literature. J Bone Joint Surg Br 2012; 94(5):584–595. doi:10.1302/0301-620X.94B5.28523
7. **Ogbonna OH, Paul Y, Nabhani H, Medina A.** Brodie's abscess in a patient presenting with sickle cell vasoocclusive crisis. Case Rep Med 2015; 2015:429876. doi:10.1155/2015/429876
8. **Bukhari A, Chen JZ, Joffe AM, Chiu I.** A painful leg lump. Clin Infect Dis 2016; 63(10):1388–1390. doi:10.1093/cid/ciw515
9. **Lowe J, Bridwell RE, Matlock AG, Cibrario A, Oliver J.** A case of Brodie's abscess with tibial erosion and extravasation into surrounding soft tissue. Cureus 2020; 12(6):e8592. doi:10.7759/cureus.8592
10. **Conterno LO, Turchi MD.** Antibiotics for treating chronic osteomyelitis in adults. Cochrane Database Syst Rev 2013; (9):CD004439. doi:10.1002/14651858.CD004439.pub3
11. **Salik M, Mir MH, Philip D, Verma S.** Brodie's abscess: a diagnostic conundrum. Cureus 2021; 13(7):e16426. doi:10.7759/cureus.16426

Address: *Masumi Suzuki Shimizu, MD, Department of Infectious Diseases, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki City, Nagasaki 852-8102, Japan; masumic2@outlook.com*

Sarah Khan, MD
Department of Internal Medicine, Cleveland Clinic, Cleveland, OH

Maureen Linganna, MD
Department of Gastroenterology, Hepatology, and Nutrition, Cleveland Clinic, Cleveland, OH; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Diagnosis and management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome

ABSTRACT

Ascites is the most common decompensation-associated complication of cirrhosis leading to reduced survival. Following significant development of antimicrobial resistance and studies comparing therapeutic options, the American Association for the Study of Liver Diseases released a new guidance providing an in-depth review of those studies and updated guidelines based on expert opinions and emerging data. We review salient 2021 guidance recommendations to provide brief pearls for diagnosis and management of ascites and relevant conditions associated with decompensated cirrhosis, such as hyponatremia, hepatic hydrothorax, spontaneous bacterial peritonitis, and hepatorenal syndrome, and use of transjugular intrahepatic shunt.

KEY POINTS

All patients with new-onset ascites, worsening distention, symptoms concerning for spontaneous bacterial peritonitis, or admitted to hospital, should undergo diagnostic paracentesis.

Sodium restriction and diuresis are the mainstay of initial ascites management. Initial diuresis should begin with spironolactone, with addition of loop diuresis if needed.

Refractory ascites may require regular large-volume paracentesis followed by albumin infusion.

doi:10.3949/ccjm.90a.22028

In response to significant advances of antimicrobial resistance and studies comparing therapeutic options for ascites and hepatorenal syndrome, the American Association for the Study of Liver Disease published a new 2021 guidance[1] as a comprehensive guide for both outpatient and inpatient diagnostic evaluation and management of ascites, updated information regarding use of albumin, and specified definitions and management recommendations for hyponatremia.

ASCITES

Development of ascites is associated with a reduction of 5-year survival from 80% to 30%,[1,2] largely associated with complications that include infection and hepatorenal syndrome. A thorough evaluation is required for diagnosis of new ascites to exclude other etiologies, including heart failure, renal failure, infections, or malignancy.[1] Complete initial analysis should consist of laboratory evaluation, abdominal Doppler ultrasonography, and a diagnostic paracentesis,[1] although no data currently support this recommendation. A serum ascites albumin gradient 1.1 g/dL or greater suggests portal hypertension, massive liver metastases, or right heart failure.[1,3] In addition to patients with symptoms suggestive of infection (eg, fevers, abdominal pain), ascitic fluid cultures should be obtained for any decompensating patient, including for the development of encephalopathy, acute kidney injury, or jaundice.[1]

ASCITES MANAGEMENT

In general, angiotensin II receptor-antagonists, angiotensin-converting enzyme inhibitors, and non-steroidal anti-inflammatory drugs should be avoided in patients with ascites owing to impact on effective circulating volume and renal perfusion.[1] Though not directly nephrotoxic, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor-antagonists was noted to correlate with increased risk of end-stage renal disease in cirrhotic patients with ascites.[4]

Based on treatment response, ascites can be classified as responsive, recurrent, or refractory.[5] Initial management of ascites includes 2 g sodium restriction. Diuresis initially with spironolactone 100 to 200 mg daily is suggested for first-time ascites, and dose adjustments should be made at intervals of at least 72 hours, up to a maximum daily dose of 400 mg.[1] For recurrent ascites, combination therapy with furosemide and spironolactone is recommended with a starting dose of 40-mg furosemide to a maximum 160-mg dose daily.[5] Once ascites has been mobilized, diuretics should be tapered to the lowest effective dose to minimize adverse effects.[1] In some cases (approximately 5% to 10% of all patients with cirrhosis), ascites cannot be managed medically and becomes refractory, with 50% survival at 6 months.[1,6]

Refractory ascites occurs when one of three criteria are met: recurrence as grade 2 or 3 within 4 weeks of mobilization with diuretic therapy (early recurrence),[1,7] persistence despite maximum diuretic dosage (diuretic resistant), or recurrence or persistence of side effects from attempting to increase diuretics (diuretic intolerant).[1]

Therapeutic large volume paracentesis (> 5 L) can be used for refractory ascites with fewer side effects than diuresis.[1,8,9] Removal of large amounts of fluid, particularly > 8 L, can lead to circulatory shifts and postparacentesis circulatory dysfunction, which manifests as hepatorenal syndrome, hepatic encephalopathy, or dilutional hyponatremia.[1,10,11] Albumin infusion with 6 to 8 g/L of ascitic fluid removed is recommended to mitigate this risk.[1,10,12]

Nonselective beta blockers, used in managing portal hypertension, are associated with higher incidence of postparacentesis circulatory dysfunction,[13,14] although there is insufficient evidence to recommend against their use in cirrhosis. Instead, caution is advised in the setting of renal insufficiency, hyponatremia, or hypotension.[15]

Transjugular intrahepatic portosystemic shunt placement is a useful treatment for refractory ascites in certain patients, particularly for those with low Model for End-stage Liver Disease scores[16] and confers a 93% chance of 1-year transplant-free survival compared with 53% for patients managed with paracenteses, diuretics, and albumin.[17] Following placement, it may take up to 6 months for ascites resolution, and so salt restriction should be continued following transjugular intrahepatic portosystemic shunt placement. It is recommended to discontinue diuretic therapy to allow return of splanchnic volume to systemic circulation. Despite good results in patients with low Model for End-stage Liver Disease scores, scores ≥ 18 are generally considered high risk for transjugular intrahepatic portosystemic shunt.[18] Patients who are not candidates for transjugular intrahepatic portosystemic shunt should be considered for referral for liver transplantation.[1,18]

Hyponatremia and hepatic hydrothorax are also frequently encountered with cirrhosis, defined as a serum sodium less than 135 mEq/L.[1,19] Seen in 49% of patients with cirrhosis, low serum sodium is associated with severe ascites and frequent ascitic complications.[19] The most common subtype is hypervolemic hyponatremia, owing to third spacing and vasopressin activation, while hypovolemic hyponatremia may occur with diuretic use.[19,20] Rate of sodium correction is based on acuity with goal rate of increase in serum sodium for chronic cases of 4 to 6 mEq/L over 24 hours.[21,22] In acute cases, correction should be faster, though the exact rate is not specified in the guidance.[1] Specific management of hyponatremia is based on severity, as follows[1,3,17,23]:

- Mild hyponatremia (126–135 mEq/L) may be monitored.[1]
- Moderate hyponatremia (120–125 mEq/L) with hypervolemia is managed with fluid restriction and diuretics. Vaptans (vasopressin receptor antagonists) are limited in use due to high cost and should be used only up to 30 days. For hypovolemic patients, normal saline and decreased diuretics may be used.[1]
- Severe hyponatremia (< 120 mEq/L) may be managed with concentrated albumin infusion. Hypertonic saline is considered in limited subsets of patients, in the critical care setting or peri-transplant.[1]

Hepatic hydrothorax, a difficult-to-manage complication of cirrhosis, is a transudative pleural effusion due to translocation of peritoneal fluid through diaphragmatic defects and reported to occur in 4% to 12% of patients with cirrhosis.[24] Though typically right-sided, it may occur on the left, bilaterally, and

in the absence of ascites.[24] It is associated with high mortality risk, exceeding that predicted by the Model for End-stage Liver Disease score.[1,3,24] Management is similar to that of ascites, with fluid restriction and diuresis.[1] Abdominal hernias, particularly umbilical hernias, are common in the setting of ascites due to increased intra-abdominal pressure. Surgical repair may be considered when ascites management and nutritional status have been optimized.[24]

SPONTANEOUS BACTERIAL PERITONITIS

The most common source of bacterial infection in patients with cirrhosis is spontaneous bacterial peritonitis (SBP), accounting for 27% to 36% of infections.[1,4,25,26] Clinical deterioration (ie, jaundice, altered mentation, or acute kidney injury) should prompt exclusion of SBP with a diagnostic paracentesis. In hospitalized patients, diagnostic paracentesis should be performed even in the absence of symptoms suggestive of SBP.[27] Diagnosis of SBP is established when the fluid absolute neutrophil count is greater than 250 cells/mm^3 and is further confirmed with positive cultures.[1,28] Empiric intravenous antibiotics after cultures are obtained are the mainstay of management of SBP and spontaneous bacterial empyema, as each hour's delay in treatment increases mortality by 10%.[1,4,5,29]

Effective empiric antibiotic choice plays a key role in timely management of SBP.[1] Third generation cephalosporins are effective if local prevalence of multidrug resistant organisms is low, while broad coverage therapy (ie, piperacillin-tazobactam with vancomycin) is recommended for high prevalence of multidrug resistant organisms, history of prior multidrug resistant organisms infection, nosocomial and hospital-acquired infections, or in critical illness. Daptomycin should be added if there is history of vancomycin-resistant *Enterococcus*. Some confusion arises with positive cultures and fewer than 250 cells/mm^3 of neutrophils; such cases do not require antibiotics and likely are contaminants.[1]

In addition to antibiotics, albumin dosed at 1.5 g/kg on day 1 and 1 g/kg on day 3 should be administered and is especially helpful if concomitant acute kidney injury or jaundice are present.[5,30,31] Repeat paracentesis/thoracentesis after 2 days of therapy may be done to assess treatment response.[1] Treatment, secondary prophylaxis with norfloxacin, or ciprofloxacin in the absence of norfloxacin, should be used. For cases of gastrointestinal hemorrhage, prophylaxis with intravenous ceftriaxone 1 g every 24 hours for 7 days should be used.[1] Primary SBP prophylaxis should also be considered in the following cases of cirrhosis without bleeding[1]:

- Ascitic protein < 1.5 g/L
- Renal dysfunction (serum creatinine ≥ 1.2 mg/dL, blood urea nitrogen > 25 mmol/L, or serum sodium < 130 mEq/L)
- Liver failure, with a Child-Turcotte-Pugh mortality predicting score greater than 9 (severity determined by a higher score ranging from good hepatic function with 5 points to advanced hepatic dysfunction with 15 points) or a bilirubin greater than 3 mg/dL.[1,7,12,30]

ACUTE KIDNEY INJURY

Patients with cirrhosis and ascites are at risk of acute kidney injury (ie, increase in creatinine ≥ 0.3 mg/dL within 48 hours or ≥ 50% increase in creatinine over 7 days), with an estimated prevalence in hospitalized patients between 27% and 53%.[1,32,33] The two most common causes of acute kidney injury are prerenal azotemia and acute tubular necrosis. Prerenal azotemia may be secondary to hypovolemia or hepatorenal syndrome. The diagnosis of hepatorenal syndrome is made once hypovolemia/shock, nephrotoxic exposure, and structural kidney damage have been excluded in a patient with ascites who presents with prerenal acute kidney injury.[1,32,33]

The principle management of hepatorenal syndrome is vasoconstrictor and albumin therapy for up to 14 days. In the United States, midodrine and octreotide in combination are used for hepatorenal syndrome therapy, though their efficacy is low.[33] The preferred treatment is terlipressin, a vasoconstrictor that may be used outside of the intensive care unit, which has been shown to improve the likelihood of reversal of hepatorenal syndrome without dialysis and 10-day survival relative to placebo (29.1% vs 15.8%; P = .012).[3,34,35] It was very recently approved in the United States in limited settings, and centers are in the process of developing protocols to incorporate its use for hepatorenal syndrome treatment.[36] An alternative with comparable efficacy is norepinephrine, though use is limited to the intensive care unit.[1] Some studies have looked into using vasopressin in place of octreotide, which has been associated with improved survival and recovery, though use in the United States has thus far been limited.[1,37]

Response to therapy may be defined as creatinine decrease to less than 1.5 mEq/L or within 0.3 mEq/L of baseline.[1] If a response is not seen on maximum doses of therapy for 4 consecutive days, vasoconstrictors may be discontinued.[1] In treatment failure, renal replacement therapy is reserved for those referred for transplant, or

based on reversibility of other organ dysfunction. In patients with limited expectation for renal recovery, dual liver-kidney transplant may be considered.

REFERENCES

1. **Biggins SW, Angeli P, Garcia-Tsao G, et al.** Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2021; 74(2):1014–1048. doi:10.1002/hep.31884
2. **Pant C, Jani BS, Desai M, et al.** Hepatorenal syndrome in hospitalized patients with chronic liver disease: results from the Nationwide Inpatient Sample 2002–2012. J Investig Med 2016; 64:33–38. doi:10.1136/jim-d-15-00181
3. **Runyon BA, Montano AA, Akriviadis EA, Antillon MR, Irving MA, McHutchison JG.** The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. Ann Intern Med 1992; 117(3):215–220. doi:10.7326/0003-4819-117-3-215
4. **Hsu WF, Yu SH, Lin JT, et al.** Renal effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with liver cirrhosis: a nationwide cohort study. Gastroenterol Res Pract 2019; 2019:1743290. doi:10.1155/2019/1743290
5. **Moore KP, Wong F, Gines P, et al.** The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology 2003; 38(1):258–266. doi:10.1053/jhep.2003.50315
6. **Moreau R, Delegue P, Pessione F, et al.** Clinical characteristics and outcome of patients with cirrhosis and refractory ascites. Liver Int 2004; 24(5):457–464. doi:10.1111/j.1478-3231.2004.0991.x
7. **Salerno F, Guevara M, Bernardi M, et al.** Refractory ascites: pathogenesis, definition and therapy of a severe complication in patients with cirrhosis [published correction appears in Liver Int 2010; 30(8):1244]. Liver Int 2010; 30(7):937–947. doi:10.1111/j.1478-3231.2010.02272.x
8. **Gines P, Arroyo V, Quintero E, et al.** Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites. Results of a randomized study. Gastroenterology 1987; 93:234–241. doi:10.1016/0016-5085(87)91007-9
9. **Bernardi M, Carceni P, Navickis RJ, Wilkes MM.** Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology 2012; 55(4):1172–1181. doi:10.1002/hep.24786
10. **Ruiz-del-Arbol L, Monescillo A, Jimenéz W, Garcia-Plaza A, Arroyo V, Rodés J.** Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. Gastroenterology 1997; 113(2):579–586. doi:10.1053/gast.1997.v113.pm9247479
11. **Tan HK, James PD, Wong F.** Albumin may prevent the morbidity of paracentesis-induced circulatory dysfunction in cirrhosis and refractory ascites: a pilot study. Dig Dis Sci 2016; 61(10):3084–3092. doi:10.1007/s10620-016-4140-3
12. **Runyon BA; AASLD.** Introduction to the revised American Association for the Study of Liver Diseases Practice guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology 2013; 57(4):1651–1653. doi:10.1002/hep.26359
13. **Sersté T, Melot C, Francoz C, et al.** Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. Hepatology 2010; 52(3):1017–1022. doi:10.1002/hep.23775
14. **Sersté T, Francoz C, Durand F, et al.** Beta-blockers cause paracentesis-induced circulatory dysfunction in patients with cirrhosis and refractory ascites: a cross-over study. J Hepatol 2011; 55(4):794–799. doi:10.1016/j.jhep.2011.01.034
15. **Reiberger T, Mandorfer M.** Beta adrenergic blockade and decompensated cirrhosis. J Hepatol 2017; 66(4):849–859. doi:10.1016/j.jhep.2016.11.001
16. **Tan HK, James PD, Sniderman KW, Wong F.** Long-term clinical outcome of patients with cirrhosis and refractory ascites treated with transjugular intrahepatic portosystemic shunt insertion. J Gastroenterol Hepatol 2015; 30(2):389–395. doi:10.1111/jgh.12725
17. **Bureau C, Thabut D, Oberti F, et al.** Transjugular intrahepatic portosystemic shunts with covered stents increase transplant-free survival of patients with cirrhosis and recurrent ascites [published correction appears in Gastroenterology 2017; 153(3):870]. Gastroenterology 2017; 152(1):157–163. doi:10.1053/j.gastro.2016.09.016
18. **Angermayr B, Cejna M, Karnel F, et al.** Child-Pugh versus MELD score in predicting survival in patients undergoing transjugular intrahepatic portosystemic shunt. Gut 2003; 52(6):879–885. doi:10.1136/gut.52.6.879
19. **Angeli P, Wong F, Watson H, Ginès P; CAPPS Investigators.** Hyponatremia in cirrhosis: results of a patient population survey. Hepatology 2006; 44(6):1535–1542. doi:10.1002/hep.21412
20. **Gines P, Guevara M, Arroyo V, Rodes J.** Hepatorenal syndrome. Lancet 2003; 362(9398):1819–1827. doi:10.1016/S0140-6736(03)14903-3
21. **Sterns RH.** Disorders of plasma sodium--causes, consequences, and correction. N Engl J Med 2015; 372(1):55–65. doi:10.1056/NEJMra1404489
22. **Mohmand HK, Issa D, Ahmad Z, Cappuccio JD, Kouides RW, Sterns RH.** Hypertonic saline for hyponatremia: risk of inadvertent overcorrection. Clin J Am Soc Nephrol 2007; 2(6):1110–1117. doi:10.2215/CJN.00910207
23. **D'Amico G, Garcia-Tsao G, Pagliaro L.** Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006; 44(1):217–231. doi:10.1016/j.jhep.2005.10.013
24. **Badillo R, Rockey DC.** Hepatic hydrothorax: clinical features, management, and outcomes in 77 patients and review of the literature. Medicine (Baltimore) 2014; 93(3):135–142. doi:10.1097/MD.0000000000000025
25. **Fernández J, Acevedo J, Castro M, et al.** Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology 2012; 55(5):1551–1561. doi:10.1002/hep.25532
26. **Piano S, Singh V, Caraceni P, et al.** Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. Gastroenterology 2019; 156(5):1368–1380.e10. doi:10.1053/j.gastro.2018.12.005
27. **Runyon BA; AASLD Practice Guidelines Committee.** Management of adult patients with ascites due to cirrhosis: an update. Hepatology 2009; 49(6):2087–2107. doi:10.1002/hep.22853
28. **Wong CL, Holroyd-Leduc J, Thorpe KE, Straus SE.** Does this patient have bacterial peritonitis or portal hypertension? How do I perform a paracentesis and analyze the results? JAMA 2008; 299(10):1166–1178. doi:10.1001/jama.299.10.1166
29. **Arabi YM, Dara SI, Memish Z, et al.** Antimicrobial therapeutic determinants of outcomes from septic shock among patients with cirrhosis. Hepatology 2012; 56(6):2305–2315. doi:10.1002/hep.25931
30. **Gatta A, Angeli P, Caregaro L, Menon F, Sacerdoti D, Merkel C.** A pathophysiological interpretation of unresponsiveness to spironolactone in a stepped-care approach to the diuretic treatment of ascites in nonazotemic cirrhotic patients. Hepatology 1991; 14(2):231–236. pmid:1860680
31. **Sort P, Navasa M, Arroyo V, et al.** Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999; 341(6):403–409. doi:10.1056/NEJM199908053410603
32. **Ginès P, Solà E, Angeli P, Wong F, Nadim MK, Kamath PS.** Hepatorenal syndrome [published correction appears in Nat Rev Dis Primers 2018; 4(1):33]. Nat Rev Dis Primers 2018; 4(1):23. doi:10.1038/s41572-018-0022-7
33. **Angeli P, Ginès P, Wong F, et al.** Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites [published

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

correction appears in J Hepatol 2015; 63(1):290]. J Hepatol 2015; 62(4):968–974. doi:10.1016/j.jhep.2014.12.029
34. **Wong F, Pappas SC, Curry MP, et al.** Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. N Engl J Med 2021; 384(9):818–828. doi:10.1056/NEJMoa2008290
35. **Wong F, Curry M, Reddy K, et al.** The CONFIRM study: a North American randomized controlled trial (RCT) of terupressin plus albumin for the treatment of hepatorenal syndrome type 1 (HRS-1) [Abstract]. Hepatology 2019; 70:1480A.
36. **US Food and Drug Administration.** FDA approves treatment to improve kidney function in adults. September 14, 2022. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-improve-kidney-function-adults-hepatorenal-syndrome. Accessed March 13, 2023.
37. **Kiser TH, Fish DN, Obritsch MD, Jung R, MacLaren R, Parikh CR.** Vasopressin, not octreotide, may be beneficial in the treatment of hepatorenal syndrome: a retrospective study. Nephrol Dial Transplant 2005; 20(9):1813–1820. doi:10.1093/ndt/gfh930

Address: *Maureen Linganna, MD, Department of Gastroenterology, Hepatology, and Nutrition, A51, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; linganm@ccf.org*

Cleveland Clinic

Improve Your Virtual Patient Visit Skills

Many patients are eager to visit their physicians virtually, but not all physicians are comfortable conducting virtual visits.

You can take advantage of a free series of self-directed online modules to help you build your virtual patient visit skills.

The free course offers:

- brief introduction to virtual visits
- guidance for demonstrating communication and empathy
- best practices for taking a patient history
- instructions for conducting a physical examination, based on organ system

To help you master the content, the free course includes many video demonstrations and knowledge checks throughout.

Visit clevelandclinic.org/virtual-training

With the exception of the physical examination module, these activities have been approved for *AMA PRA Category 1 Credit™*.

Michelle M. Kittleson, MD, PhD
Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA; Writing Committee Member, 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Heart failure with reduced ejection fraction: What's new in the 2022 guideline?

ABSTRACT

The 2022 guideline from the American College of Cardiology, American Heart Association, and Heart Failure Society of America provides practical recommendations for preventing, diagnosing, and managing patients with heart failure. This article summarizes the most important of these recommendations, specifically for managing patients with heart failure with reduced ejection fraction (HFrEF), and how they should change daily practice.

KEY POINTS

- Optimal guideline-directed medical therapy for HFrEF comprises the combination drug containing the neprilysin inhibitor sacubitril and the angiotensin II receptor blocker (ARB) valsartan; an evidence-based beta-blocker; a mineralocorticoid antagonist; and a sodium-glucose cotransporter 2 inhibitor.
- Sacubitril-valsartan is preferred over angiotensin-converting enzyme (ACE) inhibitors and ARBs based on evidence from randomized controlled trials that it increases survival rates and reduces hospitalizations in patients with HFrEF. ACE inhibitors should be used only in patients who cannot tolerate sacubitril-valsartan, and ARBs used only in those who cannot receive sacubitril-valsartan or an ACE inhibitor.
- Patients with HFrEF receiving guideline-directed medical therapy whose ejection fraction increases to more than 40% should continue to receive guideline-directed medical therapy.

doi:10.3949/ccjm.90a.22101

Heart failure is a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood. It can be classified in several ways, eg, by stage, effect of symptoms on function, and ejection fraction (**Table 1**). These classification schemes are important because the underlying causes, clinical trajectories, and effective therapies differ depending on these factors.

Stage C heart failure, in which patients develop symptoms of heart failure, requires the greatest focus and attention because these patients have high morbidity and mortality rates. In addition, for stage C heart failure with reduced ejection fraction (HFrEF) in particular, there is a wealth of evidence-based and guideline-based medical therapy to help patients feel better, stay out of the hospital, live longer, and potentially improve left ventricular function. Thus, stage C HFrEF and the 2022 guideline for treating it[1] will be the focus of this article.

WHO WROTE THE GUIDELINE?

The 2022 guideline was developed by the American College of Cardiology, American Heart Association, and Heart Failure Society of America. It provides updated evidence-based recommendations[1] and supersedes the 2013 full guidelines[2] and the 2016[3] and 2017[4] focused updates.

TABLE 1
Classifications of heart failure

Stages

A At risk of heart failure due to conditions such as hypertension, diabetes, coronary artery disease
B Pre-heart failure with no symptoms but evidence for structural heart disease including reduced ejection fraction, increased left ventricular wall thickness, valvular disease
C Symptomatic heart failure with structural heart disease and heart failure symptoms
D Advanced heart failure with marked symptoms despite attempts at optimization of guideline-directed medical therapy

New York Heart Association symptom classes

I No symptoms
II Symptoms with moderate exertion
III Symptoms with mild exertion
IV Symptoms with minimal exertion or at rest

Ejection fraction categories

Reduced: ≤ 40%
Mildly reduced: 41%–49%
Preserved: ≥ 50%
Improved: > 40% after initially being ≤ 40%

Classes of recommendation

The recommendations all receive a class (strength) of recommendation based on evidence from randomized controlled trials, nonrandomized analyses, and expert opinion. The recommendation classes are as follows:

- Class 1. Strong: there is evidence or general agreement that a given treatment or procedure is beneficial, useful, or effective.
- Class 2a. Moderate: the weight of evidence favors the treatment's usefulness or utility.
- Class 2b. Weak: the treatment's usefulness or efficacy is less well established by evidence or opinion.
- Class 3. No benefit: there is evidence or general agreement that the treatment or procedure is not useful or effective and in some cases may be harmful.

Class 1 and class 2a recommendations should be incorporated into clinical practice.

WHAT ARE THE MAIN RECOMMENDATIONS?

The 2022 guideline is 159 pages long (including 40 pages of references) and contains 14 sections, 33 tables, 15 figures, and 192 recommendations. Specifically for stage C HFrEF, the high-yield recommendations include the following[5]:

Sacubitril-valsartan is recommended in patients with HFrEF and New York Heart Association (NYHA) class II or III symptoms to reduce morbidity and mortality (class 1 recommendation).

Even if a patient with chronic HFrEF and class II or III symptoms is already receiving an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) and tolerating it well, replacing it with sacubitril-valsartan is recommended to further reduce morbidity and mortality (class 1 recommendation).

Beta-blockers. In patients with HFrEF with current or previous symptoms, use of 1 of the 3 beta-blockers proven to reduce mortality risk (bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended to reduce mortality risk and hospitalizations (class 1 recommendation).

Mineralocorticoid antagonists. In patients with HFrEF and class II to IV symptoms, a mineralocorticoid antagonist (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if the estimated glomerular filtration rate is higher than 30 mL/min/1.73 m^2 and the serum potassium level is less than 5.0 mmol/L. Serum potassium, renal function, and diuretic dosing should be carefully monitored at initiation and every 3 to 6 months thereafter to minimize the risks of hyperkalemia and renal insufficiency (class 1 recommendation).

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are recommended in patients with symptomatic chronic HFrEF to reduce hospitalizations for heart failure and cardiovascular mortality, regardless of whether the patient has type 2 diabetes (class 1 recommendation).

If the ejection fraction improves after treatment, guideline-directed medical therapy should be continued to prevent relapse of heart failure and left ventricular dysfunction, even in patients who no longer have symptoms (class 1 recommendation).

For patients self-identified as Black with class III or IV symptomatic HFrEF who are receiving optimal medical therapy, the combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality (class 1 recommendation).

Ivabradine. For patients with symptomatic (class II to III) stable chronic HFrEF (left ventricular ejection fraction ≤ 35%) who are receiving guideline-directed medical therapy including a beta-blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of at least 70 beats per minute at rest, the addition of ivabradine (which inhibits the "funny" current of the sinoatrial node, reducing heart rate without reducing contractility) can be beneficial to reduce heart failure hospitalizations and cardiovascular death (class 2a recommendation).

WHAT IS DIFFERENT FROM PREVIOUS GUIDELINES?

Sacubitril-valsartan instead of ACE inhibitors and ARBs

The role of ACE inhibitors in HFrEF was established in the 1980s in patients with NYHA class IV heart failure,[6] with subsequent trials demonstrating their superiority over isosorbide dinitrate-hydralazine[7] and in less-sick patients with NYHA class I, II, or III symptoms.[8,9] ACE inhibitors became a cornerstone of HFrEF management in the late 1980s.

And they still would be, were it not for recognition of the importance of another important neurohormonal axis in heart failure, ie, the natriuretic peptide system, which promotes natriuresis, diuresis, and vasodilation—all good things.

While the now-defunct recombinant natriuretic peptide nesiritide offered no benefit in HFrEF,[10] another way to increase natriuretic peptide levels is by inhibiting their degradation by neprilysin. Sacubitril inhibits neprilysin, but it also increases angiotensin, so it had to be combined with an inhibitor of the renin-angiotensin system. While an ACE inhibitor would be the preferred choice for this job, the combination of sacubitril and an ACE inhibitor, both of which also increase bradykinin by inhibiting its degradation, would pose a prohibitive risk of angioedema,[11] which is why sacubitril is combined with valsartan, an ARB.

This theoretical benefit was tested in a randomized trial pitting sacubitril-valsartan against enalapril.[12] In this trial, 93% of patients were on beta-blockers, and 55% were on mineralocorticoid antagonists. The publication of this trial in 2014 marked the end of the reign of ACE inhibitors: compared with enalapril, sacubitril-valsartan demonstrated greater reduction in cardiovascular death and heart failure hospitalization. At a median of 27 months, when the trial was stopped early because of benefit, this combined end point had occurred in 26.5% in the enalapril group vs 21.8% in the sacubitril-valsartan group (hazard ratio 0.80, 95% confidence interval 0.73–0.87, $P < .001$).[12] This translates to a number needed to treat of 21 patients for 27 months to prevent 1 death or heart failure hospitalization.

The 2022 guideline reflects these advances, providing a class 1 recommendation for sacubitril-valsartan over an ACE inhibitor or ARB in patients with chronic symptomatic HFrEF.

SGLT-2 inhibitors get a class 1 indication in HFrEF

In 2008, the US Food and Drug Administration announced that, to be approved, any new therapy for type 2 diabetes must demonstrate cardiovascular safety.[13] Subsequently, multiple medications in the new class of SGLT-2 inhibitors were run through the gauntlet of cardiovascular outcome trials. It was an unexpected boon when, between 2015 and 2020, multiple SGLT-2 inhibitors were deemed not only safe but also effective in reducing atherosclerotic events and—even more unexpectedly—heart failure.[14–17]

The world was therefore ready when in 2019 dapagliflozin was found to decrease the incidence of cardiovascular death and heart failure hospitalization in patients with HFrEF without diabetes.[18] Good news soon followed from empagliflozin in 2020.[19] The 2022 guideline emphasizes the significant impact of SGLT-2 inhibition in heart failure, giving this class of drugs a class 1 indication in HFrEF in patients with or without type 2 diabetes.

The importance of comprehensive guideline-directed medical therapy

The 2022 guideline also highlights the importance of comprehensive guideline-directed medical therapy for HFrEF with sacubitril-valsartan, an evidence-based beta-blocker, a mineralocorticoid antagonist, and an SGLT-2 inhibitor. Use of all 4 drug classes is estimated to reduce all-cause mortality in HFrEF by 73% compared with no treatment, and over 2 years, the number needed to treat would be 3.9 patients to prevent

1 death or heart failure hospitalization.[20] Furthermore, an estimated 6.3 years of life is saved with use of all 4 drugs compared with just 2 (an ACE inhibitor and a beta-blocker) in patients ages 55 to 65.[21]

The 2022 guideline includes value statements created for select recommendations where high-quality, cost-effectiveness studies of the intervention have been published. Interventions with high value include treatment with sacubitril-valsartan instead of an ACE inhibitor as well as treatment with an evidence-based beta-blocker and mineralocorticoid in all patients with HFrEF. Treatment with an SGLT-2 inhibitor was deemed of intermediate economic value with a projection of high economic value if drug costs were reduced.

Don't stop if ejection fraction improves

Heart failure with improved ejection fraction is a recently defined[22] and clinically meaningful category of heart failure. Whether patients whose ejection fraction improves while receiving guideline-directed medical therapy should keep receiving it was not clear until a landmark trial randomized such patients to continue or stop.[23] In this trial, heart failure recurred only in those patients in whom guideline-directed medical therapy was withdrawn.

With adjunctive therapies, it is essential to avoid "indication creep," the inappropriate application of therapies to unproven uses

There is now a class 1 recommendation that patients with heart failure with improved ejection fraction after treatment should continue guideline-directed medical therapy to prevent relapse of heart failure and left ventricular dysfunction, even patients whose symptoms have gone away.[1]

Complementary therapies

Isosorbide dinitrate-hydralazine. In the 1980s, to assess whether the hemodynamic benefit of afterload translates into clinical benefit, a number of trials of vasodilatory therapy were done in patients with HFrEF. In 1986, a randomized trial demonstrated that prazosin was no better than placebo. The mortality rate was numerically lower with isosorbide dinitrate-hydralazine than with placebo, but the difference was not quite statistically significant ($P = .053$).[24]

While isosorbide dinitrate-hydralazine was ultimately bested by ACE inhibitors,[7] a subgroup analysis demonstrated significant benefit in patients who self-described as Black.[25] This hypothesis-generating signal was later confirmed: Black patients with HFrEF and NYHA class III or IV symptoms had higher survival rates with isosorbide dinitrate-hydralazine compared with placebo.[26]

With adjunctive therapies, it is essential to avoid "indication creep," the inappropriate application of therapies to unproven uses. For example, approximately 90% of enrolled patients in this trial were on ACE inhibitors and 70% were on beta-blockers. Thus, isosorbide dinitrate-hydralazine is not a substitute for optimal quadruple therapy in patients with HFrEF, but as adjunctive therapy in Black patients with blood pressure high enough to tolerate isosorbide dinitrate-hydralazine after initiation and optimization of guideline-directed medical therapy.

Ivabradine. Observational studies of patients with HFrEF noted an inverse relationship between heart rate and survival, with higher survival rates in patients with lower heart rates.[27] A meta-analysis of the randomized trials of beta-blockers in HFrEF also noted that those patients with greater lowering of heart rate had better survival.[28] Of course, these observations could be association (patients with lower heart rate and able to tolerate higher-dose beta-blocker treatment are less sick) rather than causation (patients with heart failure do better if they have a lower heart rate).

The medication ivabradine offered the possibility to assess the impact of heart-rate-lowering in HFrEF. By inhibiting I_f (the funny current in the sinoatrial node), ivabradine reduces heart rate without reducing contractility, thus theoretically allowing greater heart-rate-lowering without the limiting hypotension and fatigue of beta-blockers.

A randomized trial tested this theory, assessing the impact of ivabradine in patients with HFrEF and a baseline heart rate of 70 beats per minute or more despite taking a beta-blocker at the highest dose they could tolerate.[29] The incidence of the primary end point (cardiovascular death or hospital admission for worsening heart failure) was 24% in the ivabradine group and 29% in the placebo group ($P < .0001$).[29]

However, it is important to avoid another potential indication creep: ivabradine is not a substitute for a beta-blocker. It has not been tested and found, by itself, to reduce the mortality rate, whereas beta-blockers have. Rather, ivabradine is an adjunctive therapy, to be added to the regimen in those who have a heart rate 70 beats per minute or more despite maximum-tolerated evidence-based beta-blocker therapy.

DO OTHER SOCIETIES AGREE OR DISAGREE?

The 2016 European Society of Cardiology guideline for the diagnosis and treatment of acute and chronic heart failure[30] offers congruent recommendations regarding optimal guideline-directed medical therapy for stage C HFrEF, including the superiority of sacubitril-valsartan over ACE inhibitors and ARBs and the need for evidence-based beta-blocker, mineralocorticoid antagonist, and SGLT-2 inhibitor therapy. Recommendations for selective use of isosorbide dinitrate-hydralazine and ivabradine are also similar.

HOW WILL THIS CHANGE DAILY PRACTICE?

The 2022 guideline emphasizes the benefit of "quadruple therapy" in patients with symptomatic HFrEF, ie, sacubitril-valsartan, an evidenced-based beta-blocker, a mineralocorticoid antagonist, and an SGLT-2 inhibitor. In clinical practice, it is essential to implement these guidelines in every patient at every visit with a stepwise approach:

Step 1. Is the patient on optimal guideline-directed medical therapy?

Step 2. If not, justify why (prior intolerance, cost, allergy) and document it.

Step 3. Is the patient on maximum-tolerated dosages of guideline-directed medical therapy?

Step 4. If not, either increase dosages in a stepwise fashion, or document why further titration is not possible (limiting heart rate, blood pressure, potassium, or creatinine). This would include stepwise initiation, every 1 to 2 weeks, of the following:

- Low-dose sacubitril-valsartan (sacubitril 24 mg and valsartan 26 mg, twice daily), followed by
- A beta-blocker (carvedilol 3.125 twice daily or metoprolol succinate 25 mg daily), then
- A mineralocorticoid antagonist (spironolactone 25 mg daily or eplerenone 50 mg daily), and
- An SGLT-2 inhibitor (dapagliflozin 10 mg daily or empagliflozin 10 mg daily).

After all 4 pillars of treatment are initiated, then sacubitril-valsartan and beta-blocker could be doubled every 1 to 2 weeks as tolerated by heart rate, blood pressure, and serum potassium and creatinine levels.

WHEN WOULD THE GUIDELINES NOT APPLY?

While optimal guideline-directed medical therapy will improve quality of life and survival of patients with HFrEF, there are important populations in whom these therapies are not indicated.

First, ensure that patients are receiving optimal quadruple therapy at maximum-tolerated doses before initiating isosorbide dinitrate-hydralazine or ivabradine (avoid the indication creep described above).

Next, be mindful of the following specific contraindications:

- Sacubitril-valsartan is contraindicated in patients with any history of angioedema, particularly in reaction to an ACE inhibitor.
- Mineralocorticoid antagonists should not be prescribed in patients with an estimated glomerular filtration rate less than 30 mL/min/1.73 m^2 or a serum potassium level higher than 5.0 mmol/L, as these medications could increase the risk of hyperkalemia hospitalizations and deaths in such patients.[31]
- SGLT-2 inhibitors are contraindicated in patients with type 1 diabetes mellitus or on dialysis.
- Finally, according to the 2022 guideline, ivabradine is not recommended in patients with atrial fibrillation, as it increases the risk of atrial fibrillation.

DISCLOSURES

The author reports no relevant financial relationships which, in the context of her contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Heidenreich PA, Bozkurt B, Aguilar D, et al.** 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2022; 79(17):e263–e421. doi:10.1016/j.jacc.2021.12.012
2. **Yancy CW, Jessup M, Bozkurt B, et al.** 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013; 128(16):e240–e327. doi:10.1161/CIR.0b013e31829e8776
3. **Yancy CW, Jessup M, Bozkurt B, et al.** 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America [published correction appears in Circulation 2016; 134(13):e298]. Circulation 2016; 134(13):e282–e293. doi:10.1161/CIR.0000000000000435
4. **Yancy CW, Jessup M, Bozkurt B, et al.** 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017; 136(6): e137–e161. doi:10.1161/CIR.0000000000000509
5. **Kittleson MM.** A clinician's guide to the 2022 ACC/AHA/HFSA

guideline for the management of heart failure. J Card Fail 2022; 28(5):831–834. doi:10.1016/j.cardfail.2022.03.346
6. **CONSENSUS Trial Study Group.** Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316(23):1429–1435. doi:10.1056/NEJM198706043162301
7. **Cohn JN, Johnson G, Ziesche S, et al.** A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991; 325(5):303–310. doi:10.1056/NEJM199108013250502
8. **SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN.** Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991; 325(5):293–302. doi:10.1056/NEJM199108013250501
9. **SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB Jr, Cohn JN.** Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions [published correction appears in N Engl J Med 1992; 327(24):1768]. N Engl J Med 1992; 327(10):685–691. doi:10.1056/NEJM199209033271003
10. **O'Connor CM, Starling RC, Hernandez AF, et al.** Effect of nesiritide in patients with acute decompensated heart failure [published correction appears in N Engl J Med 2011; 365(8):773]. N Engl J Med 2011; 365(1):32–43. doi:10.1056/NEJMoa1100171
11. **Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E.** Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs Enalapril (OCTAVE) trial. Am J Hypertens 2004; 17(2):103–111. doi:10.1016/j.amjhyper.2003.09.014
12. **McMurray JJ, Packer M, Desai AS, et al; PARADIGM-HF Investigators and Committees.** Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014; 371(11):993–1004. doi:10.1056/NEJMoa1409077no
13. **US Food and Drug Administration.** Department of Health and Human Services. Guidance for industry on diabetes mellitus-evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes; availability. Federal Register 2008; 73(245):77724–77725.
14. **Neal B, Perkovic V, Mahaffey KW, et al.** Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017; 377(7):644–657. doi:10.1056/NEJMoa1611925
15. **Zinman B, Wanner C, Lachin JM, et al.** Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373(22):2117–2128. doi:10.1056/NEJMoa1504720
16. **Wiviott SD, Raz I, Bonaca MP, et al.** Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019; 380(4):347–357. doi:10.1056/NEJMoa1812389
17. **Cannon CP, Pratley R, Dagogo-Jack S, et al.** Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020; 383(15):1425–1435. doi:10.1056/NEJMoa2004967
18. **McMurray JJV, Solomon SD, Inzucchi SE, et al.** Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019; 381(21):1995–2008. doi:10.1056/NEJMoa1911303
19. **Packer M, Anker SD, Butler J, et al.** Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020; 383(15):1413–1424. doi:10.1056/NEJMoa2022190
20. **Bassi NS, Ziaeian B, Yancy CW, Fonarow GC.** Association of optimal implementation of sodium-glucose cotransporter 2 inhibitor therapy with outcome for patients with heart failure. JAMA Cardiol 2020; 5(8):948–951. doi:10.1001/jamacardio.2020.0898
21. **Vaduganathan M, Claggett BL, Jhund PS, et al.** Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomized controlled trials. Lancet 2020; 396(10244):121–128. doi:10.1016/S0140-6736(20)30748-0
22. **Bozkurt B, Coats AJ, Tsutsui H, et al.** Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail 2021; S1071-9164(21)00050-6. doi:10.1016/j.cardfail.2021.01.022
23. **Halliday BP, Wassall R, Lota AS, et al.** Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet 2019; 393(10166):61–73. doi:10.1016/S0140-6736(18)32484-X
24. **Cohn JN, Archibald DG, Ziesche S, et al.** Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration cooperative study. N Engl J Med 1986; 314(24):1547–1552. doi:10.1056/NEJM198606123142404
25. **Carson P, Ziesche S, Johnson G, Cohn JN.** Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. J Card Fail 1999; 5(3):178–187. doi:10.1016/s1071-9164(99)90001-5
26. **Taylor AL, Ziesche S, Yancy C, et al.** Combination of isosorbide dinitrate and hydralazine in blacks with heart failure [published correction appears in N Engl J Med 2005; 352(12):1276]. N Engl J Med 2004; 351(20):2049–2057. doi:10.1056/NEJMoa042934
27. **Fox K, Ford I, Steg PG, et al.** Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomized controlled trial. Lancet 2008; 372(9641):817–821. doi:10.1016/S0140-6736(08)61171-X
28. **McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW.** Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. Ann Intern Med 2009; 150(11):784–794. doi:10.7326/0003-4819-150-11-200906020-00006
29. **Swedberg K, Komajda M, Böhm M, et al.** Ivabradine and outcomes in chronic heart failure (SHIFT): a randomized placebo-controlled study [published correction appears in Lancet 2010; 376(9757):1988]. Lancet 2010; 376(9744):875–885. doi:10.1016/S0140-6736(10)61198-1
30. **Ponikowski P, Voors AA, Anker SD, et al.** 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Kardiol Pol 2016; 74(10):1037–1147. Polish. doi:10.5603/KP.2016.0141
31. **Juurlink DN, Mamdani MM, Lee DS, et al.** Rates of hyperkalemia after publication of the randomized Aldactone Evaluation Study. N Engl J Med 2004; 351(6):543–551. doi:10.1056/NEJMoa040135

Address: *Michelle M. Kittleson, MD, PhD, Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, 8670 Wilshire Blvd., 2nd floor, Los Angeles, CA 90211; Michelle.kittleson@cshs.org*

CME MOC

Ilyssa O. Gordon, MD, PhD
Department of Pathology, Robert J. Tomsich Pathology & Laboratory Medicine Institute and Sustainability, Buildings+Design, Cleveland Clinic, Cleveland, OH; Associate Professor of Pathology, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Neil Mehta, MD
Department of Internal Medicine and Geriatrics, Cleveland Clinic, Cleveland, OH; Professor of Medicine and Associate Dean, Curricular Affairs, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

J. Harry Isaacson, MD
Department of Internal Medicine and Geriatrics, Cleveland Clinic, Cleveland, OH; Professor of Medicine and Executive Dean, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Sumita B. Khatri, MD
Department of Pulmonary Medicine, Cleveland Clinic, Cleveland, OH; Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

How does climate change impact our patients?

Physicians are increasingly aware of the health harms associated with climate change.[1–3] Both climate change and air pollution are driven by emission of greenhouse gases, including carbon dioxide, which trap heat in the atmosphere (**Figure 1**).[4,5] Although the resultant harms affect nearly every organ system,[6] gaps exist between the evidence of harm and clinical practices that address it. Patients may lack knowledge about the specific health impacts and risks of climate change, but they are receptive to learning more.[2] Indeed, government agencies and nonprofit health organizations make climate change and health information readily available to the public and encourage patients to ask their doctors about their own risks and how to avoid harm.[7]

One need not be a climate and health expert to empower patients to learn more and to work with them to protect their health. Clinicians at all levels of experience can integrate climate-related health information and counseling into their practices.[8] In this Commentary, we address 3 disease areas where climate influence on health is relevant to the clinical practice setting—cardiovascular, respiratory, and infectious disease—and offer important resources to share with patients (**Tables 1 and 2**).

CARDIOVASCULAR HEALTH AND CLIMATE

Heat is the leading weather-related killer in the United States and is implicated in deaths caused by cardiovascular disease,[9,10] and more than one-third of deaths worldwide are attributable to climate change.[11] With the increasing frequency and duration of heat waves,[12] more patients will experience cardiovascular morbidity. Further, despite physiologic adaptations intended to dissipate heat,[13] heat exposure places acute demands on the cardiovascular system that can lead to ischemia and heart failure, especially in patients with pre-existing cardiac conditions.[14]

Medication adjustments

Many common medications have the side effect of temperature dysregulation, and some medications contribute to dehydration during heat exposure (see sidebar, "**Climate change and patient care**"). For example, diuretics cause blood volume loss, antihypertensives lower blood pressure, and antidepressants can increase perspiration.[15] Other medications may reduce sweating and dysregulate thermoregulation, contributing to heat-related illness.[16]

Medication storage may be a concern. Exposure to heat and humidity decreases the effectiveness of some prescription and over-the-counter drugs.[17] Such concerns should be shared with the patient and a joint decision made regarding whether alternative medications are appropriate.

Avoiding and responding to heat-related illness

Any patient, including those with pre-existing cardiovascular disease, who exercises or works outdoors should be educated to recognize an impaired physiologic response to heat.[18,19] Heat-related illness presents on a spectrum that may range from muscle cramps to seizure, with muscle cramps being an early warning sign. Heat exhaustion is characterized by heavy sweating that progresses to headache, nausea, weakness, and dizziness. Heat stroke presents with altered mental status, loss of consciousness, and seizure.

Treatment of heat-related illness includes applying cold water or ice to the skin. Heat stroke, where there is a risk of multiorgan failure and death, requires cold water immersion and emergency medical care.[20]

Outdoor activity should be avoided during midday and early afternoon. The "urban heat-island effect" is a factor in locations where pavement and vehicular traffic are abundant, and outdoor activity should be avoided in

doi:10.3949/ccjm.90a.22007

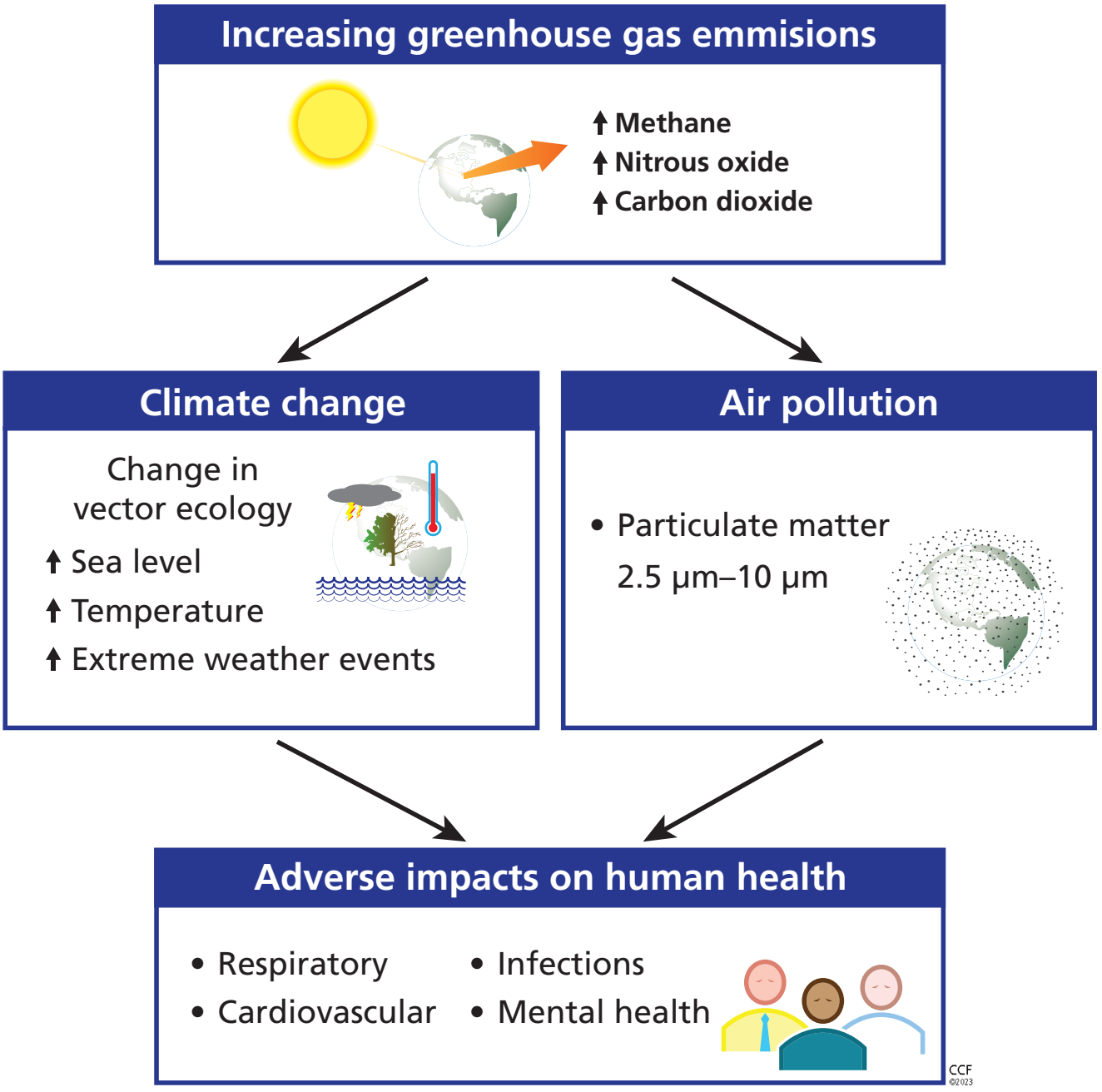


Figure 1. Greenhouse gas emissions are increasing, leading to climate change and air pollution, which both adversely impact human health.

those locations. Patients who must engage in outdoor activity on high-heat days should be encouraged to drink plenty of water before and during activity.

RESPIRATORY DISEASE AND AIR QUALITY

Asthma, chronic obstructive pulmonary disease, and allergies comprise a large proportion of primary care.[21] These can be exacerbated by heat, extreme weather events such as wildfires and flood, air pollution, and allergens—all of which are increasing due to climate change.[22]

Air quality basics

Polluted air consists of hundreds of interrelated substances that form mostly in association with indus-

TABLE 1
Climate influence on health: What patients can do

Disease area	Climate change consequences	Patient actions
Cardiovascular	Increased risk of heart attack, stroke, ischemic heart disease, heart failure	Avoid going out during midday heat
		Exercise early in the morning and in the shade
	Increased risk of heat-related illness during exercise	Be aware of signs of heat-related illness: eg, heart racing, nausea, headache, muscle cramping
Respiratory	Increased potency of allergic inflammatory response	Check air quality index on a weather app or bookmarked website
	Increased asthma and chronic obstructive pulmonary disease symptoms and exacerbations	Follow simple measures to improve indoor air quality, such as removing shoes and dusting
Infectious	Changing distribution of infectious disease-bearing vectors	Wear appropriate clothing to reduce skin and hair exposure
	Increased survival and breeding of disease-bearing vectors	Be aware of possible disease-bearing ticks and mosquitos in the area, use insect repellent, and check for ticks after being outdoors

TABLE 2
Climate change and health: Resources for patients

Cardiovascular disease
- US Department of Labor. Occupational Safety and Health Administration. Heat. https://www.osha.gov/heat-exposure
- Centers for Disease Control and Prevention. Natural Disasters and Severe Weather. Extreme heat. https://www.cdc.gov/disasters/extremeheat/index.html

Respiratory disease
- US Air Quality Index. AirNow. https://www.airnow.gov/
- American Lung Association. Clean Air. https://www.lung.org/clean-air

Infectious disease
- US Centers for Disease Control and Prevention. Climate effects on health: Diseases carried by vectors. https://www.cdc.gov/climateandhealth/effects/vectors.htm

trial and traffic-related emissions from burning fossil fuels. Ozone, derived from sunlight interacting with other air pollutants, is one of 6 common or "criteria" air pollutants,[23] while others are particulate matter, carbon monoxide, lead, sulfur dioxide, and nitrogen dioxide. Known as "smog" when present at ground level, ozone can potentiate oxidative stress, particularly when airways are inflamed, as in asthma and chronic obstructive pulmonary disease.[24] For individuals with allergies, exposure to ozone pollution can increase the potency of the allergic inflammatory response.[25]

Climate change aggravates these factors by altering the seasons so that allergen-producing plants have longer growth and flowering periods and therefore higher allergenicity.[26] Enhanced ozone formation is associated with high-heat days, and longer ozone seasons are associated with more prominent asthma symptoms[27,28] and a higher incidence of asthma in children who play outdoor sports.[29] The environmental impact may have direct effects on the bronchial epithelium, or the effects may be mediated by epigenetic mechanisms, interactions that set the stage for disease occurrence and increased severity of disease.[30]

Managing the response to air quality

Patients who have chronic respiratory disease can be reminded to check local outdoor air-quality conditions, including smog levels, and to limit outdoor activities (see sidebar, "**Climate change and patient care**").

Indoor air quality should not be overlooked when counseling patients, given the vast amount of time that many people spend indoors. Indoor air pollution levels may be 2 to 5 times greater than outdoor levels.[31,32] Exposure to indoor gas stoves is associated with increased risk of asthma and asthma symptoms in children, and gas stoves produce nitrogen dioxide, a criteria pollutant.[33]

Outdoor air pollution also influences indoor air quality. Infiltration occurs when the home "envelope" is not airtight, such as with suboptimal insulation. Natural ventilation occurs when windows and doors are open, and mechanical ventilation occurs when rooms or appliances are connected to the outdoors through ductwork.[31] To improve indoor air quality[34] and reduce respiratory disease exacerbations,[35] patients can be advised to do the following:

- Use an air purifier
- Close windows that face roadways
- Remove shoes at entryways
- Properly ventilate a gas stove or switch to an electric stove
- Evaluate chemicals used in home cleaning.

Medication adjustments

Alternative choices might be appropriate for patients who need prescription inhalers. Inhaled corticosteroids and dry-powder inhalers are better options than metered-dose inhalers. The propellants in metered-dose inhalers are themselves greenhouse gases.[36]

INFECTIOUS DISEASE

Global warming is expected to significantly impact the distribution of infectious diseases because of its effects on vectors (usually arthropods such as ticks and mosquitoes) or habitats and behaviors of animal hosts. The likely result will be unfamiliar vector-borne illnesses in previously unaffected locations.

In addition to climate change, factors that affect vectors and host animals include discontinuation of the use of dichloro-diphenyl-trichloroethane (DDT) in the 1960s, deforestation, and increasing travel and global trade.[37] It can be difficult to isolate the specific effects of climate change, but there is evidence that it will increase the spread of vector-borne illness.[38] For example, arthropods are cold-blooded creatures that survive better in warmer climates, and increased rain and water collection will increase their breeding sites.

Evolution of infection spread

Changes in ecosystems and sea level may drive migration of humans and animal hosts, introducing diseases into new areas.[39] The following are several examples:

- **Mosquito migration.** *Anopheles aegypti*, a mosquito, is the primary vector that spreads dengue virus, Zika virus, yellow fever, and Chikungunya. This mosquito prefers warm climates and is spreading from its traditional tropical habitat. *Anopheles albopictus* (tiger mosquito), also a vector for these diseases, can survive in colder climates and is found in North America and Europe.[40] A visitor infected with one of these diseases can introduce it into a nonendemic area, where it can then be spread by *A albopictus*, and a local outbreak can result.[41]
- **Changing Canadian weather.** The *Ixodes* tick in its nymphal stage is the vector for Lyme disease. Meteorologic variables such as heat and humidity affect tick activity, accounting for their spread into southern Canada.[42] The white-footed mouse, the primary reservoir host for *Borrelia burgdorferi*, is migrating into Canada in response to shorter, milder winters.[43]
- **Mosquito- and tick-borne spread.** West Nile virus infection was first reported in the United States in 1999 in the New York City area. Spread primarily by the *Culex* mosquito, it has now been reported in every US state.[44] Eastern equine encephalitis (mosquito-borne) and Powassan virus infection (tick-borne) are rare arthropod-transmitted infections. They are present in limited areas in North America but could spread over time, similar to West Nile virus.[45,46]

Similar presentations

Common to these infections are fever, rash, headache, joint pain, and neurologic symptoms. When encountering patients with these signs and symptoms, the differential diagnosis should include emerging infectious diseases (see sidebar, **"Climate change and patient care"**). Limited exposure to these diseases during clinical training and day-to-day practice underscores the need for vigilance and consideration when the clinical context is appropriate.

INCREASING PATIENT AWARENESS OF CLIMATE'S EFFECTS ON HEALTH

The increasing frequency and intensity of extremely hot weather, worsening air pollution, and changing

CLIMATE CHANGE AND PATIENT CARE

Scenario 1: Chronic lung disease and cardiac risk

An 86-year-old patient presents with worsening shortness of breath. An ex-smoker with a history of hypertension and hypothyroidism, the patient is afebrile and has new lower-extremity swelling. A chest radiograph shows findings consistent with emphysema, and thyroid-stimulating hormone and B-type natriuretic peptide levels are both mildly elevated. The management plan includes prescriptions for an inhaler and diuretic, and an adjusted thyroid medication dose.

Climate implications. You note that the outdoor temperature is 89°F with high humidity and poor air quality and, upon questioning, you learn that the patient has no air conditioning at home. The high temperature is a risk for a patient with pulmonary and cardiovascular disease. Further, certain medications can contribute to temperature dysregulation and be damaged by high temperature and humidity. Accordingly, you prescribe a dry-powder inhaler instead of a metered-dose inhaler and advise the patient regarding:

- Access to cooling centers
- Medication storage (eg, thyroid medication) in a space protected from heat
- The need to check the air quality index and ambient temperature before going outside
- Awareness of signs of heat stress.

Scenario 2: A young patient with possible infection

A 14-year-old presents with fever, headache, joint pain, and fatigue. A maculopapular "sunburn" type of rash is noted on the extremities. A COVID-19 test is negative. Being in a midwestern US state, you initially consider a limited differential diagnosis of influenza, Lyme disease, and West Nile virus. The patient's guardian mentions that no one else at home has been sick.

Climate implications. You ask whether the family has been affected by recent flooding in the area, and learn that they have been forced to spend more time outdoors while mold-mitigation was under way in the home due to flood damage. With this information, you consider the likelihood of an increase in the local mosquito population due to standing water and extend the differential diagnosis to include emerging mosquito-borne illnesses in the Midwest, such as eastern equine encephalitis, dengue virus, and Chikungunya. You advise the patient and their family regarding:

- Use of mosquito repellents
- Wearing clothing that covers the arms and legs when outdoors
- Removing sources of standing water outdoors.

vector habitats are some of the effects of climate change that will change the scope of cardiovascular, respiratory, and infectious disease. Awareness of risk factors associated with climate change will enhance our ability to provide effective care for patients with existing chronic illness and those with new onset of disease. Knowledge about the health effects of climate change will enhance our ability to consider the consequences of climate change in our differential diagnoses and gain confidence in counseling patients on mitigation of these harmful effects. Comprehensive patient health and well-being will benefit from our understanding of the effects of climate change on health.

DISCLOSURES

Dr. Gordon has disclosed research grants from Celgene, GB004, Morphic Therapeutics, Pfizer, Pliant, and UCB. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Kotcher J, Maibach E, Miller J, et al.** Views of health professionals on climate change and health: a multinational survey study. Lancet Planet Health 2021; 5(5):e316–e323. doi:10.1016/S2542-5196(21)00053-X
2. **Hathaway J, Maibach EW.** Health implications of climate change: a review of the literature about the perception of the public and health professionals. Curr Environ Health Rep 2018; 5(1):197–204. doi:10.1007/s40572-018-0190-3
3. **United States Environmental Protection Agency.** Greenhouse gas emissions. Updated May 16, 2022. https://www.epa.gov/ghgemissions/overview-greenhouse-gases. Accessed March 15, 2023.
4. **West JJ, Smith SJ, Silva RA, et al.** Co-benefits of global greenhouse gas mitigation for future air quality and human health. Nat Clim Chang 2013; 3(10):885–889 doi:10.1038/NCLIMATE2009
5. **Sarfaty M, Mitchell M, Bloodhart B, Maibach EW.** A survey of African American physicians on the health effects of climate change. Int J Environ Res Public Health 2014; 11(12):12473–12485. doi:10.3390/ijerph111212473
6. **Salas RN, Solomon CG.** The climate crisis—health and care delivery. N Engl J Med 2019; 381(8):e13. doi:10.1056/NEJMp1906035
7. **Asthma and Allergy Foundation of America.** Climate and health. https://aafa.org/advocacy/key-issues/climate-and-health/. Accessed March 17, 2023.
8. **Senay E, Sarfaty M, Rice MB.** Strategies for clinical discussions about climate change. Ann Intern Med 2021; 174(3):417–418. doi:10.7326/M20-6443

9. **United States Environmental Protection Agency.** Climate change indicators: heat-related deaths. Updated August 2, 2022. https://www.epa.gov/climate-indicators/climate-change-indicators-heat-related-deaths. Accessed March 15, 2023.
10. **Khatana SAM, Werner RM, Groeneveld PW.** Association of extreme heat and cardiovascular mortality in the United States: a county-level longitudinal analysis from 2008 to 2017. Circulation 2022; 146(3):249–261. doi:10.1161/CIRCULATIONAHA.122.060746
11. **Vicedo-Cabrera AM, Scovronick N, Sera F, et al.** The burden of heat-related mortality attributable to recent human-induced climate change. Nat Clim Chang 2021; 11(6):492–500. doi:10.1038/s41558-021-01058-x
12. **Intergovernmental Panel on Climate Change.** Climate change 2021: the physical science basis. https://www.ipcc.ch/report/sixth-assessment-report-working-group-i/. Accessed March 15, 2023.
13. **Mora C, Counsell CWW, Bielecki CR, Louis LV.** Twenty-seven ways a heat wave can kill you: deadly heat in the era of climate change. Circ Cardiovasc Qual Outcomes 2017; 10(11):e004233. doi:10.1161/CIRCOUTCOMES.117.004233
14. **Cramer MN, Gagnon D, Laitano O, Crandall CG.** Human temperature regulation under heat stress in health, disease, and injury. Physiol Rev 2022; 102(4):1907–1989. doi:10.1152/physrev.00047.2021
15. **Bongers KS, Salahudeen MS, Peterson GM.** Drug-associated non-pyrogenic hyperthermia: a narrative review. Eur J Clin Pharmacol 2020; 76(1):9–16. doi:10.1007/s00228-019-02763-5
16. **Westaway K, Frank O, Husband A, et al.** Medicines can affect thermoregulation and accentuate the risk of dehydration and heat-related illness during hot weather. J Clin Pharm Ther 2015; 40(4):363–367. doi:10.1111/jcpt.12294
17. **Ougi K, Okada K, Leong KH, Hayashi Y, Kumada S, Onuki Y.** Effect of the molecular mobility of water adsorbed by disintegrants on storage-induced hydrolytic degradation of acetylsalicylic acid incorporated into tablets under humid conditions. Eur J Pharm Sci 2020; 154:105502. doi:10.1016/j.ejps.2020.105502
18. **Ebi KL, Capon A, Berry P, et al.** Hot weather and heat extremes: health risks. Lancet 2021; 398(10301):698–708. doi:10.1016/S0140-6736(21)01208-3
19. **De Blois J, Kjellstrom T, Agewall S, Ezekowitz JA, Armstrong PW, Atar D.** The effects of climate change on cardiac health. Cardiology 2015; 131(4):209–217. doi:10.1159/000398787
20. **Douma MJ, Aves T, Allan KS, et al.** First aid cooling techniques for heat stroke and exertional hyperthermia: a systematic review and meta-analysis. Resuscitation 2020; 148:173–190. doi:10.1016/j.resuscitation.2020.01.007
21. **Finley CR, Chan DS, Garrison S, et al.** What are the most common conditions in primary care? Systematic review. Can Fam Physician 2018; 64(11):832–840. pmid:30429181
22. **D'Amato G, Cecchi L, D'Amato M, Annesi-Maesano I.** Climate change and respiratory diseases. Eur Respir Rev 2014; 23(132):161–169. doi:10.1183/09059180.00001714
23. **United States Environmental Protection Agency.** Criteria air pollutants. Updated August 9, 2022. https://www.epa.gov/criteria-air-pollutants. Accessed March 15, 2023.
24. **Sahiner UM, Birben E, Erzurum S, Sackesen C, Kalayci Ö.** Oxidative stress in asthma: part of the puzzle. Pediatr Allergy Immunol 2018; 29(8):789–800. doi:10.1111/pai.12965
25. **Khatri SB, Holguin FC, Ryan PB, Mannino D, Erzurum SC, Teague WG.** Association of ambient ozone exposure with airway inflammation and allergy in adults with asthma. J Asthma 2009; 46(8):777–785. pmid:19863280
26. **Anderegg WRL, Abatzoglou JT, Anderegg LDL, Bielory L, Kinney PL, Ziska L.** Anthropogenic climate change is worsening North American pollen seasons. Proc Natl Acad Sci U S A 2021; 118(7):e2013284118. doi:10.1073/pnas.2013284118
27. **Schnell JL, Prather MJ.** Co-occurrence of extremes in surface ozone, particulate matter, and temperature over eastern North America. Proc Natl Acad Sci U S A 2017; 114(11):2854–2859. doi:10.1073/pnas.1614453114
28. **Schwarz L, Hansen K, Alari A, et al.** Spatial variation in the joint effect of extreme heat events and ozone on respiratory hospitalizations in California. Proc Natl Acad Sci U S A 2021; 118(22):e2023078118. doi:10.1073/pnas.2023078118
29. **McConnell R, Berhane K, Gilliland F, et al.** Asthma in exercising children exposed to ozone: a cohort study [published correction appears in Lancet 2002; 359(9309):896]. Lancet 2002; 359(9304):386–391. doi:10.1016/S0140-6736(02)07597-9
30. **Yang IV, Lozupone CA, Schwartz DA.** The environment, epigenome, and asthma. J Allergy Clin Immunol 2017; 140(1):14–23. doi:10.1016/j.jaci.2017.05.011
31. **United States Environmental Protection Agency.** The inside story: a guide to indoor air quality. Updated November 22, 2022. https://www.epa.gov/indoor-air-quality-iaq/inside-story-guide-indoor-air-quality. Accessed March 15, 2023.
32. **Wallace LA, Pellizzari ED, Hartwell TD, Whitmore R, Sparacino C, Zelon H.** Total exposure assessment methodology (TEAM) study: personal exposures, indoor-outdoor relationships, and breath levels of volatile organic compounds in New Jersey. Environ Int 1986; 12(1–4):369–387.
33. **Lin W, Brunekreef B, Gehring U.** Meta-analysis of the effects of indoor nitrogen dioxide and gas cooking on asthma and wheeze in children. Int J Epidemiol 2013; 42(6):1724–1737. doi:10.1093/ije/dyt150
34. **Vardoulakis S, Giagloglou E, Steinle S, et al.** Indoor exposure to selected air pollutants in the home environment: a systematic review. Int J Environ Res Public Health 2020; 17(23):8972. doi:10.3390/ijerph17238972
35. **Subramanian A, Khatri SB.** The exposome and asthma. Clin Chest Med 2019; 40(1):107–123. doi:10.1016/j.ccm.2018.10.017
36. **Wilkinson A, Woodcock A.** The environmental impact of inhalers for asthma: a green challenge and a golden opportunity. Br J Clin Pharmacol 2022; 88(7):3016–3022. doi:10.1111/bcp.15135
37. **Patz JA, Confalonieri EC, Amerasinghe FP, et al.** Human health: ecosystem regulation of infectious diseases. In: Hassan R, Scholes R, Ash N, eds. Ecosystems and human well-being: current state and trends. Washington, DC: Island Press; 2005:391–415.
38. **Rocklöv J, Dubrow R.** Climate change: an enduring challenge for vector-borne disease prevention and control [published correction appears in Nat Immunol 2020; 21(6):695]. Nat Immunol 2020; 21(5):479–483. doi:10.1038/s41590-020-0648-y
39. **El-Sayed A, Kamel M.** Climatic changes and their role in emergence and re-emergence of diseases. Environ Sci Pollut Res Int 2020; 27(18):22336–22352. doi:10.1007/s11356-020-08896-w
40. **Romi R, Severini F, Toma L.** Cold acclimation and overwintering of female Aedes albopictus in Roma. J Am Mosq Control Assoc 2006; 22(1):149–151. doi:10.2987/8756-971X(2006)22[149:CAAOOF]2.0.CO;2
41. **Morin CW, Comrie AC, Ernst K.** Climate and dengue transmission: evidence and implications. Environ Health Perspect 2013; 121(11-12):1264–1272. doi:10.1289/ehp.1306556
42. **Moore SM, Eisen RJ, Monaghan A, Mead P.** Meteorological influences on the seasonality of Lyme disease in the United States. Am J Trop Med Hyg 2014; 90(3):486–496. doi:10.4269/ajtmh.13-0180
43. **Roy-Dufresne E, Logan T, Simon JA, Chmura GL, Millien V.** Poleward expansion of the white-footed mouse (Peromyscus leucopus) under climate change: implications for the spread of lyme disease. PLoS One 2013; 8(11):e80724. doi:10.1371/journal.pone.0080724
44. **Centers for Disease Control and Prevention.** West Nile virus, statistics & maps. Updated January 11, 2023. https://www.cdc.gov/westnile/statsmaps/index.html. Accessed March 15, 2023.
45. **Ludwig A, Zheng H, Vrbova L, Drebot MA, Iranpour M, Lindsay LR.** Increased risk of endemic mosquito-borne diseases in Canada due to climate change. Can Commun Dis Rep 2019; 45(4):91–97. doi:10.14745/ccdr.v45i04a03
46. **Hassett EM, Thangamani S.** Ecology of Powassan Virus in the United States. Microorganisms 2021; 9(11):2317. doi:10.3390/microorganisms9112317

***Address**: Ilyssa O. Gordon, MD, PhD, Department of Pathology, Robert J. Tomsich Pathology & Laboratory Medicine Institute, L4-146, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; gordoni@ccf.org*

COMMENTARY

Pelin Batur, MD, FACP, NCMP
Department of Subspecialty Women's Health, Ob/Gyn and Women's Health Institute, Cleveland Clinic, Cleveland, OH; Professor, Ob/Gyn and Reproductive Biology, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH; Deputy Editor, *Cleveland Clinic Journal of Medicine*

Paternalism in practice: How we create obstacles for sexual, reproductive, and menopausal healthcare despite our best intentions

Pa·ter·nal·ism: *the policy or practice on the part of people in positions of authority of restricting the freedom and responsibilities of those subordinate to them in the subordinates' supposed best interest*.[1]

Hopefully, you haven't judged this article by the title, because the aim is not to single out any gender, as we have *all* likely made paternalistic recommendations to patients based on our personal beliefs or fears, as opposed to evidence-based principles. As I reflect on close to 30 years of patient care, I have seen many examples of this within my field of women's health.

In theory, we all understand the concept of shared decision-making, but in practice, clinical recommendations are often still dictated, as opposed to being discussed. Patients are now better informed than ever before and may wish to discuss a variety of options. A perceived lack of choice has led patients to seek alternative sources for care, some of which may be harmful owing to less evidence or regulation. If a treatment is not within the doctor's comfort zone, of course there should be no obligation to prescribe. But in many circumstances, there are lost opportunities to align plans more closely with patient's priorities. Using specific women's health topics as representative examples, this article aims to show how clinical care may be improved using 3 principles: humility, advocacy, and flexibility.

MENOPAUSE MANAGEMENT: A CASE FOR HUMILITY

The evolution of the evidence on menopausal hormone therapy (MHT) safety and the response of the medical community to the unfolding of these data are great examples of the need for humility when proclaiming what we know to be medical "truth." After years of observational data suggesting strong cardiovascular benefits of MHT use, the initial results of the Women's Health Initiative (WHI) randomized placebo-controlled trial,[2] outlining the risks and benefits of MHT use, brought shockwaves to the clinical care of women, landing on the 2002 covers of Newsweek and Time magazines. Before this landmark trial, 1 of every 5 US women over the age of 40 was using MHT, and after this publication, close to 90% of women discontinued their hormones.[3] As doctors' offices were flooded with phone calls, the medical community was wondering how could we have been so wrong?

Those of us working as menopause specialists were trying to explain the limitations of the WHI data to colleagues, the subgroups with lesser risks, etc., but I suspect we sounded like rambling anarchists to the vast majority of clinicians who had already decided that MHT was associated with far too much risk to justify its use. But just because MHT was no longer "in," this did not change the fact that women were continuing to suffer with symptoms. Patients were encouraged to tough it out until symptoms subsided (which on average lasts over 7 years for most, and about a decade for Black women)[4] or go on nonhormonal treatment alternatives that were not nearly as effective and had their own list of side effects. As a US medical community, we tend to be risk-averse, which left many feeling that mainstream medicine had turned its back on them. This became fertile ground to foster an entire new industry of wellness clinics promoting the use of custom compounded hormones

doi:10.3949/ccjm.90a.22094

that came with big claims, celebrity endorsements, no scary package inserts, and potential for serious harm, including a possible increased endometrial cancer risk compared with conventional US Food and Drug Administration (FDA)-approved MHT.[5]

So was the observational evidence really so wrong?

Not really. Even though a full discussion on MHT is beyond the scope of this commentary, it is important to note that strong observational studies had shown 30% to 50% lower cardiovascular risk in MHT users, with an already known small increase in breast cancer risk.[6,7] As follow-up WHI publications were published over 20 years, the main messaging about the results evolved significantly. Initial concerns in 2002 about "substantial risks for cardiovascular disease and breast cancer"[8] were followed in 2003 by "the suggestion of a slight overall increase" in the risk of coronary heart disease (CHD),[9] changed in 2007 to "with no apparent increase in CHD risk for women close to menopause" and "total mortality reduced among women aged 50 to 59 years,"[10] and in 2017 to "no adverse influence on CHD, venous thromboembolism, or all-cause mortality" (for Black postmenopausal women with a hysterectomy).[11]

The grand finale is that US and European cardiac medical societies, who were often the most concerned about MHT risks, now note the acceptable safety profile in newly menopausal women (defined as women in their 40s and 50s or within a decade of menopause), specifically highlighting the favorable benefits of lower rates of diabetes, insulin resistance, and fracture.[12,13] It is again accepted that the time when MHT is initiated and the type of formulation used can guide whether there is an overall better risk-benefit ratio. Even the WHI authors noted how their own data have been used "inappropriately" in making decisions about treatment for women in their 40s and 50s who have distressing symptoms.[14] MHT is again officially considered an acceptable alternative to prevent fracture in those with low bone density,[15] though it has never come off my list of offered options.

But what about breast cancer risk?

We still see similar "lumping" of MHT fears regarding breast cancer risk, even though the 20-year WHI follow-up clearly shows that individuals using estrogen alone in this trial had a significant reduction in breast cancer incidence and mortality.[16] Though estrogen is not recommended for breast cancer prevention in those at high risk of developing breast cancer, it is notable that the medications used for this purpose, tamoxifen and aromatase inhibitors, have not yet shown a similar reduction in breast cancer mortality. The addition of a progestin to the MHT did indeed increase breast cancer risk after 3 to 5 years in the WHI study,[7] although other randomized controlled trials (RCTs) and observational studies have not shown similar risk increases.[6] The increase in breast cancer risk when progestin is used beyond 5 years is within the medical "rare" category of risk (less than 1 of 1,000 cases),[6,7] comparable to the increase in breast cancer risk seen with the consumption of a few alcoholic drinks per week. This degree of risk is considered acceptable to many patients who are carefully counseled in clinic.

No harm in avoiding hormones, right?

Interpreting the MHT data over time has not been easy. Discussions of complex data and concerns of scary diagnoses like heart disease and cancer make these conversations difficult to implement in a busy practice. With clinicians not having either the expertise or the time to address these concerns in clinic, not only were thousands of symptomatic women ill cared for, but also several generations of trainees were without exposure to menopause management with MHT. Most of us in menopausal medicine have noted colleagues making strong recommendations for our mutual patients to discontinue MHT, which had been prescribed after careful weighing of risks and benefits (including those practicing in a completely unrelated medical specialty, often causing a disproportionate degree of alarm for the patient). Given that several RCTs have suggested a 30% reduction in mortality with MHT use,[6] it is estimated that denial of estrogen-only therapy (with its better safety profile compared with estrogen-progestin therapy) may have led to more than 91,000 women who underwent hysterectomy (who would have needed estrogen alone) dying prematurely between 2002 and 2011.[17]

It has been 20 years since the first WHI publication, yet continuity of care in menopause clinics remains problematic, as there are far too few of us trained or certified in menopausal medicine (lists available at **menopause.org**). Every day, well-intentioned yet overly protective advice continues to unnecessarily limit MHT use in appropriate candidates. Luckily, the tide is turning, and new generations of trainees are being exposed to the most updated information, recognizing that there is an age-related window of opportunity for MHT use. In other words, when patients start therapy in their 40s or 50s, or within a decade of menopause, benefits are optimized, and risks are lower.

Unfortunately, this acceptance has come a little too late, with at least one-third of patients navigating toward unregulated products that can cause supraphysiologic hormone levels. We regularly see women in our clinics with male testosterone levels after compounded use of discouraged treatments such as hormone injections or pellets. It is important to help guide these patients back toward clinicians who are prescribing MHT in a safer, evidence-based approach, with adequate counseling about potential risks. Yet some patients have simply lost faith in "mainstream" medical care. Strong fluctuations in recommendations for or against a therapy over time (with exaggerated discussions of risks, while minimizing potential benefits) breed distrust not only in the clinician but also in the science itself. Most developments in medicine, when interpreted within the context of limitations, typically do not show that we were previously wrong but rather add pieces to a puzzle that make the picture clearer.

The humility lessons learned from the MHT story clearly concede that we are likely to be surprised by how medicine evolves and must acknowledge our patients' right to have open conversations and consider treatments that deviate from current mainstream thinking. We need to remember that even the most "true" medical recommendations may change with the evidence (aspirin use is a good example). Both risks *and benefits* of a treatment should be clearly discussed and the individual empowered to make their decision based on their own value system.

TREATING SEXUAL DYSFUNCTION: A CASE FOR ADVOCACY

Close to half of US women report some sort of sexual dysfunction that is reported as distressing in 1 out of 8.[18] Despite this, there were no treatments for hypoactive sexual desire disorder (HSDD) until the approval of the oral drug flibanserin in 2015.

Approval for flibanserin was tumultuous, as the FDA had unanimously rejected approval twice before. Before 2015, there were already 7 products to enhance male sexual health on the market. (I am not including testosterone, because it was not labeled for use for male low libido, although commonly used in clinical practice for that reason.) The FDA committee published its concerns about flibanserin, including "medicalizing" low sexual desire,[19] an argument that I believe questions the impact and validity of the HSDD diagnosis. Concerns about effectiveness were raised, even though the most validated tool to assess sexual health, the Female Sexual Function Index, had shown improvement. The committee noted that "an effect on daily recall of sexual desire was preferable,"[19] with a value judgment made that the primary end point of number of satisfying sexual events was not improved enough (despite recommendations otherwise by sexual health experts). In clinical practice, the most important factors to assess a woman's sexual health are more closely tied to what is measured on the Female Sexual Function Index (desire, arousal, lubrication, orgasm, satisfaction, and pain) as well as validated distress scoring systems, as opposed to the number of extra times she chooses to have sex that month.[19] If she had sex only one additional time, yet was happy with that outcome based on increased satisfaction and decreased distress, why would we think this is not good enough for her?

But shouldn't we protect female patients from harm?

Other FDA concerns were related to safety and tolerability. Before approval, there were several unusual stipulations imposed, most notably being subjected to additional studies focused on alcohol interactions with *substantial* alcohol servings (≥ 5 units). More specifically, individuals were asked to fast overnight, eat a light breakfast, then drink the alcohol equivalent of at least half a bottle of wine (typically within 10 minutes), while taking a dose of flibanserin (though package labeling calls for nighttime dosing). In these initial studies (some which consisted predominantly of men), concerns about orthostasis and hypotension prompted a risk evaluation and mitigation strategy, mandating that only certified prescribers and pharmacies could treat the patient, and that patients sign paperwork promising to avoid *any* alcohol intake.

I believe that all of this played a role in few pharmacists becoming certified due to unsubstantiated concerns (eg, that this could be used as a "date-rape drug") based on discussions on pharmacy LISTSERVs. In the postmarketing experience, we understand that alcohol use in real-world situations does not cause any more hypotension than placebo, and flibanserin has a side-effect profile that is comparable to, if not less than, that in women taking antidepressant medications (most common side effects are sedation and nausea).[20,21]

Barriers to wider uptake

There have been jokes made about flibanserin use. If it has minimal benefit but is going to make you nauseated and put you to sleep, what's the point? Yet for a woman distressed by her HSDD, who has chronic

insomnia and would like some of the appetite-suppressing effects of the medication (which may lead to ≥ 5% body weight loss),[21] it can be a great adjunct to her care, alongside traditional biopsychosocial management of sexual dysfunction. Postmarketing safety experience has allowed for the strict alcohol restrictions to be lifted, and package labeling now indicates only the need to space the medication and last drink apart by 2 hours. However, widespread utilization of flibanserin remains limited by cost and ongoing concerns about safety, and the need to avoid all alcohol is still noted within the top results following a quick Internet search.

Lack of awareness of flibanserin has also contributed to low uptake. Part of the FDA approval was contingent on the company agreeing to not run commercial advertisements for 18 months after its approval, with continued strict marketing oversight since that time.[22] As we hold this medication to a high standard of advertising ethics (which isn't a bad thing), my brain is bombarded with images of couples holding hands in adjoining bathtubs, one of the estimated 500 billion US television advertising impressions on erectile dysfunction between 2006 and 2009.[23] These advertisements have been criticized for their explicit content and lack of regulation; further, depending on the venue or timing, they have exposed minors to developmentally inappropriate information approximately 20% of the time—despite recommendations otherwise by the American Academy of Pediatrics.[23] Companies making male erectile dysfunction treatments have been some of the top spenders in direct-to-consumer advertising, leading to widespread use of these medications both clinically and recreationally, and they have even been linked to an increase in birth rates associated with television promotion.[24]

Holding female and male sexual health products to the same standards

So how is this tied to advocacy? It is important that female and male sexual health products are held to the same standards.

When the initial approval of sildenafil was fast-tracked in 1998, it was known to cause deaths when taken with nitrates, and hypotension when taken with alpha-blockers. However, female products have been subjected to unusually selective protocols and additional safety procedures. We now have a second FDA-approved treatment for HSDD, bremelanotide, self-administered by subcutaneous injection. Although bremelanotide was approved in 2019, insurance coverage remains a major barrier for both treatment options.

In contrast, there are 26 FDA-approved products for male sexual dysfunction. The concern is not simply the difference in number of treatment options between the sexes, but also the struggles of the approval and marketing processes, which have led some sexual health experts to raise concerns about paternalism within the FDA—ie, men get the choice of whether medication risks are worth it, and women need an additional layer of "protection" from harm.[25] I hesitate to speak negatively of any processes to ensure safety, but what is clear to me is that the voices of advocacy groups likely had a role in moving the approval process along, so much so that the FDA committee members felt compelled to publish their perspective and defend their processes in the *New England Journal of Medicine*.[19]

The approval process for first-in-class treatments for a new medical indication is clearly challenging. However, it is equally important to note that different sociocultural backgrounds and beliefs can contribute to biases, leading to differences in interpretation of overall treatment risk vs benefit,[25] and I suspect biases impact even more so the topic of female sexuality.

We need to advocate for more treatment options for HSDD, several of which are currently being studied. Even though RCTs have consistently shown the benefits and tolerability of testosterone replacement in women (when used at physiologic doses), the FDA has unanimously rejected the request to approve a testosterone patch. Ten US and international professional societies have come to the consensus that testosterone replacement may be tried for female HSDD, with several clinical recommendations on safe use.[26] Because there continues to be no FDA-approved way to replace testosterone in women, doing this safely remains a challenge,[27] again steering women toward unregulated and potentially harmful treatments such as high-dose pellets. And yes, these products have celebrity endorsements.

FAMILY PLANNING: A CASE FOR FLEXIBILITY

Like politics and religion, the topic of women's reproductive rights ignites passionate debates. The road to family-planning autonomy has been met with hurdles of all sorts, far too many to address here. In the absence of effective contraception, every time a female has sex with a sperm-producing partner (consensual or not), she may perceive it as a risk to her life, health, finances, career, or social support net-

TABLE 1
US Centers for Disease Control and Prevention Medical Eligibility Criteria for contraceptive use

Pre-existing condition	Contraceptive method											
	Cu-IUD		LNG-IUD		Implant		DMPA		POP		CHC	
	I	C	I	C	I	C	I	C	I	C	I	C
Nonmigraine headache (mild, severe)	1		1		1		1		1		1[a]	
Migraine without aura (includes menstrual migraine)	1		1		1		1		1		2[a]	
Migraine with aura	1		1		1		1		1		4[a]	
Stroke (history of cerebrovascular accident)	1		2		2	3	3		2	3	4	

1 No restriction (method can be used)
2 Advantages generally outweigh theoretical or proven risks
3 Theoretical or proven risks usually outweigh advantages
4 Unacceptable health risks (method not to be used)

[a] Additional stroke risk factors may change recommendation, shared decision-making advised.

C = continuing treatment; CHC = combined hormonal contraceptive; Cu-IUD = copper intrauterine device; DMPA = depot medroxyprogesterone acetate; I = initiating treatment; LNG-IUD = levonorgestrel intrauterine device; POP = progestin-only pill

Based on information in reference 28.

works. (For brevity, I'm referring to female or women as those individuals capable of becoming pregnant.) Effective contraception is underutilized among some of the women who need it the most: those with complex medical histories.

The establishment of the US Centers for Disease Control and Prevention (CDC) Medical Eligibility Criteria has been a great resource for clinicians who want to expand their knowledge of appropriate candidates for various contraceptive methods.[28] However, the pink and red sections of the CDC Medical Eligibility Criteria tables that show potential contraindications to a method in the setting of various medical comorbidities (**Table 1**)[28] can cause clinicians to be overly restrictive in their prescribing. For example, the use of estrogen-containing combined hormonal contraceptives (CHCs) in those who have migraines with aura is strongly discouraged because of a potential increased stroke risk (though absolute risks are low with the use of modern methods).[29] Certainly, for pregnancy prevention alone, if a progestin-only option is tolerated, that would be preferred. However, women may need (or prefer) CHCs to treat a medical condition, in which case the risk-benefit ratio changes. Not uncommonly, I will prescribe a method with a known contraindication, but only after a detailed discussion about pros and cons of different contraceptives—and after the patient verbalizes understanding and provides consent.[29,30]

Two guiding principles of reproductive care

As a consultant for the contraceptive and hormonal needs of our medically complex patients, I follow 2 guiding principles in managing patient care. First, the contraceptive that the patient prefers is the one she is most likely to use after she leaves my office. Second, no matter what the risks of any contraceptive, the risks of an unintended pregnancy are always far greater. Fortunately, some guidelines do soften language to address necessary variations in practice (eg, newer migraine guidelines since the publication of the CDC eligibility criteria) and emphasize the importance of shared decision-making, as opposed to a universal recommendation to withhold CHCs in those with migraine with aura.[29,31]

The contraceptive that the patient prefers is the one she is most likely to use, and whatever the risks of any contraceptive, the risks of an unintended pregnancy are always far greater

In the absence of contraindications, clinicians also withhold prescriptions because patients are not up-to-date with health screenings such as Papanicolaou tests or breast examinations. Removing barriers to effective contraception is not only evidence-based, it is also encouraged by guidelines.[32] For example, to qualify a patient for CHCs, a prescriber needs only

a medical history and a recent blood pressure reading, which can be obtained outside of the office. With excessive restrictions from doctors' offices, patients have turned to online prescribing companies that use online questionnaires to offer CHCs in an evidence-based way, with an average appointment time of 7.5 minutes, for a total average yearly cost of $313 per prescription, including cost of visit and 1 year of refills.[33] There has been a call for more widespread expansion of over-the-counter contraceptives, which is already a reality in many US states but has had slow uptake. Thus, improving access with virtual visits is encouraged, especially visits during nonbusiness hours.

Fear as an obstacle

The fear of a serious thrombotic complication from a preventive medication in a young healthy woman is understandable. The US medical-legal environment is a hostile one. Between 2008 and 2015, approximately $2 billion in litigation was disputed against the most popular CHC of that time, with ads on social networking platforms soliciting participation in lawsuits directed at the manufacturer, as opposed to individual clinicians.[34] (Interestingly, settlements were related to risks clearly outlined in the product package insert.) I suspect that much of the litigation was not related to altruistic concerns about safety, as the evidence is not convincing of a major difference in risk of this CHC compared with others, but was instead attracted by the "deep pockets" of the pharmaceutical company producing the brand- name pill. Not surprisingly, the lawsuits quickly fizzled after the medication became generic.

We cannot let medical-legal fears get in the way of listening to the patient and providing for her contraceptive choices. Flexibility in addressing contraceptive preferences is now even more critical in the setting of limited access to abortion throughout different regions of the country.

CARING FOR EACH INDIVIDUAL PATIENT

Throughout my career, I may have raised the eyebrows of some colleagues who considered my prescribing to be careless, when in fact that prescription was written after careful thought and discussion, but ultimately leaving the final decision in the hands of the informed person that is impacted most by that prescription. In embracing flexibility and humility in practice, I have moved another step away from paternalistic care, which I believe has positively affected the lives of those I have had the privilege to care for. I hope this article moves me one step closer to being a better advocate.

DISCLOSURES

The author reports no relevant financial relationships which, in the context of her contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Oxford English Dictionary.** 'art, n. 1.' OED online. Oxford University Press.
2. **Rossouw JE, Anderson GL, Prentice RL, et al.** Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33
3. **Sprague BL, Trentham-Dietz A, Cronin KA.** A sustained decline in postmenopausal hormone use: results from the National Health and Nutrition Examination Survey, 1999–2010. Obstet Gynecol 2012; 120(3):595–603. doi:10.1097/AOG.0b013e318265df42
4. **Avis NE, Crawford SL, Greendale G, et al.** Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med 2015; 175(4):531–539. doi:10.1001/jamainternmed.2014.8063
5. **Davis R, Batur P, Thacker HL.** Risks and effectiveness of compounded bioidentical hormone therapy: a case series. J Womens Health (Larchmt) 2014; 23(8):642–648. doi:10.1089/jwh.2014.4770
6. **Lipold LD, Batur P, Kagan R.** Is there a time limit for systemic menopausal hormone therapy? Cleve Clin J Med 2016; 83(8):605–612. doi:10.3949/ccjm.83a.15161
7. **Pederson HJ, Batur P.** Use of exogenous hormones in those at increased risk for breast cancer: contraceptive and menopausal hormones in gene carriers and other high-risk patients. Menopause 2023; 30(3):341-347. doi:10.1097/GME.0000000000002136
8. **Rossouw JE, Anderson GL, Prentice RL, et al.** Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288(3):321–333. doi:10.1001/jama.288.3.321
9. **Manson JE, Hsia J, Johnson KC, et al.** Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003; 349(6):523–534. doi:10.1056/NEJMoa030808
10. **Rossouw JE, Prentice RL, Manson JE, et al.** Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause [published correction appears in JAMA 2008; 299(12):1426]. JAMA 2007; 297(13):1465–1477. doi:10.1001/jama.297.13.1465
11. **Chlebowski RT, Barrington W, Aragaki AK, et al.** Estrogen alone and health outcomes in black women by African ancestry: a secondary analyses of a randomized controlled trial. Menopause 2017; 24(2):133–141. doi:10.1097/GME.0000000000000733
12. **El Khoudary SR, Aggarwal B, Beckie TM, et al.** Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. Circulation 2020; 142(25):e506–e532. doi:10.1161/CIR.0000000000000912
13. **Maas AHEM, Rosano G, Cifkova R, et al.** Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists [published correction appears in Eur Heart J 2022; 43(25):2372]. Eur Heart J 2021; 42(10):967–984. doi:10.1093/eurheartj/ehaa1044
14. **Manson JE, Kaunitz AM.** Menopause management—getting clinical care back on track. N Engl J Med 2016; 374(9):803–806. doi:10.1056/NEJMp1514242
15. **The NAMS 2017 Hormone Therapy Position Statement Advisory Panel.** The 2017 hormone therapy position statement of the North American Menopause Society. Menopause 2017; 24(7):728–753. doi:10.1097/GME.0000000000000921

16. **Chlebowski RT, Anderson GL, Aragaki AK, et al.** Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative randomized clinical trials. JAMA 2020; 324(4):369–380. doi:10.1001/jama.2020.9482
17. **Sarrel PM, Njike VY, Vinante V, Katz DL.** The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. Am J Public Health 2013; 103(9):1583–1588. doi:10.2105/AJPH.2013.301295
18. **Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB.** Sexual problems and distress in United States women: prevalence and correlates. Obstet Gynecol 2008; 112(5):970–978. doi:10.1097/AOG.0b013e3181898cdb
19. **Joffe HV, Chang C, Sewell C, et al.** FDA approval of flibanserin—treating hypoactive sexual desire disorder. N Engl J Med 2016; 374(2):101–104. doi:10.1056/NEJMp1513686
20. **Millheiser L, Clayton AH, Parish SJ, Kingsberg SA, Kim NN, Simon JA.** Safety and tolerability of evening ethanol consumption and bedtime administration of flibanserin in healthy premenopausal female subjects. Sex Med 2019; 7(4):418–424. doi:10.1016/j.esxm.2019.08.003
21. **Kingsberg SA, McElroy SL, Clayton AH.** Evaluation of flibanserin safety: comparison with other serotonergic medications. Sex Med Rev 2019; 7(3):380–392. doi:10.1016/j.sxmr.2018.12.003
22. **Department of Health and Human Services.** The Office of Prescription Drug Promotion (OPDP) of the US Food and Drug Administration (FDA). Warning letter to Sprout Pharmaceuticals, Reference ID: 4664256. https://www.fda.gov/media/142146/download. Accessed March 2, 2023.
23. **Arnold DG, Oakley JL.** The politics and strategy of industry self-regulation: the pharmaceutical industry's principles for ethical direct-to-consumer advertising as a deceptive blocking strategy. J Health Polit Policy Law 2013; 38(3):505–544. doi:10.1215/03616878-2079496
24. **Kim T, Diwas KC.** Can Viagra advertising make more babies? Direct-to-consumer advertising on public health outcomes. J Marketing Research 2020; 57(4) 599–616.
25. **Dooley EM, Miller MK, Clayton AH.** Flibanserin: from bench to bedside. Sex Med Rev 2017; 5(4):461–469. doi:10.1016/j.sxmr.2017.06.003
26. **Davis SR, Baber R, Panay N, et al.** Global consensus position statement on the use of testosterone therapy for women [published correction appears in Climacteric 2019; 22(6):637]. Climacteric 2019; 22(5):429–434. doi:10.1080/13697137.2019.1637079
27. **Smith T, Batur P.** Prescribing testosterone and DHEA: the role of androgens in women. Cleve Clin J Med 2021; 88(1):35–43. doi:10.3949/ccjm.88a.20030
28. **Curtis KM, Tepper NK, Jatlaoui TC, et al.** US medical eligibility criteria for contraceptive use, 2016. Updated recommendations MMWR Recomm Rep 2016; 65(3):1–103. doi:10.15585/mmwr.rr6503a1
29. **Batur P, Yao M, Bucklan J, et al.** Use of combined hormonal contraception and stroke: a case-control study of the impact of migraine type and estrogen dose on ischemic stroke risk. Headache 2023. [Epub ahead of print] doi:10.1111/head.14473
30. **Calhoun AH, Batur P.** Combined hormonal contraceptives and migraine: an update on the evidence. Cleve Clin J Med 2017; 84(8):631–638. doi:10.3949/ccjm.84a.16033
31. **Sheikh HU, Pavlovic J, Loder E, Burch R.** Risk of stroke associated with use of estrogen containing contraceptives in women with migraine: a systematic review. Headache 2018; 58(1):5–21. doi:10.1111/head.13229
32. **Batur P, Berenson AB.** Are breast and pelvic exams necessary when prescribing hormonal contraception? Cleve Clin J Med 2015; 82(10):661–663. doi:10.3949/ccjm.82a.15055
33. **Jain T, Schwarz EB, Mehrotra A.** A study of telecontraception. N Engl J Med 2019; 381(13):1287–1288. doi:10.1056/NEJMc1907545
34. **Batur P, Casey PM.** Drospirenone litigation: does the punishment fit the crime? J Womens Health (Larchmt) 2017; 26(2):99–102. doi:10.1089/jwh.2016.6092

***Address**: Pelin Batur, MD, FACP, NCMP, Ob/Gyn and Women's Health Institute, A8-406, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; baturp@ccf.org*

Cleveland Clinic

Ultrasound Workshop: Diagnostic and Procedural Skills

Focus on the Hospitalized Patient

May 10-13, 2023

Cleveland Clinic Simulation and Advanced Skills Center
Cleveland, OH

Hemodynamic Assessment of the Critically Ill Patient Saturday, May 13

You'll Want To Be At This Workshop

The use of ultrasound to diagnose and guide procedures is growing rapidly and you don't want to be left behind. This growth is primarily fueled by data indicating that ultrasound can improve the success rate of various procedures while decreasing complications. This ultrasound workshop will provide you with current state-of-the-art techniques for diagnosis and guiding procedures. You will be able to incorporate the lessons you learn by attending this workshop into your clinical practice.

Stay Current With These Objectives

Wednesday Optional Workshop	2-Day Course	Saturday Optional Workshops
• Building a Point-of-Care Ultrasound Program • Describe the components of successful point-of-care ultrasound programs • Summarize process for image acquisition, machine utilization, and IT configuration • Describe the importance of a training, quality improvement, and credentialing • List components of billing and coding for various ultrasound exams	• Summarize the basic science and diagnostic use of ultrasound imaging • Describe the protocols, evaluation, and best use of echocardiography in critically ill patients • Review the role of ultrasound in a focused assessment with sonography in trauma (FAST) exam to assess for free fluid in the abdomen or around the heart • Summarize the basics of using ultrasound to assess lungs • Describe the most effective diagnostic use of ultrasound to assess for vascular abnormalities including aortic pathology and deep venous thrombosis • Practice the evaluation of shock and respiratory failure with point-of-care echocardiography • Demonstrate competence in ultrasound guidance for needle placement and peripheral intravenous access, arterial line access, and midline access • Demonstrate the best use of ultrasound for paracentesis, thoracentesis, and arthrocentesis • Describe the fundamentals of tunneling technique and the tunneled CVC kit • List the indications, complications, and aftercare related to insertion of a tunneled central venous catheter (CVC) • Demonstrate competence in central venous access including materials, ultrasound landmarks, and needle placement	**Airway Management in the Critically Ill Patient** • Summarize the Cleveland Clinic Airway Management protocol and algorithm for critically ill patients • Apply airway management tools to secure the airway • Demonstrate application of the airway management protocol • Choose the best strategy to manage the airway in critically ill patients **Pediatric Simulations and Ultrasound** • Detail the causes of hypoxemia in the critically ill neonate • Effectively manage undifferentiated shock in the neonate and infant • Describe tips and tricks for vascular access in the pediatric population **Hemodynamic Assessment of the Critically Ill Patient** • Identify the hemodynamically compromised patient • Describe the 3 components of the Rapid Ultrasound for Shock and Hypotension (RUSH) exam: Pump, Tank, Pipes • Utilize the Rapid Ultrasound for Shock and Hypotension (RUSH) exam protocol • Explain the ultrasound findings seen in the 4 types of distributive shock

Who Should Attend

This workshop is designed for physicians, physician assistants, and nurse practitioners in emergency medicine, internal medicine, hospital medicine, critical care, cardiology, general surgery, pediatrics, pulmonology, anesthesiology, and radiology.

Register Today! ccfcme.org/GoUltra

This activity is approved for *AMA PRA Category 1 Credit™*, ANCC Contact Hours, and AAPA Category 1 CME Credits.

REVIEW

Alise K. Carlson, MD
Neuroimmunology Fellow, Mellen Center, Cleveland Clinic, Cleveland, OH

Daniel Ontaneda, MD, PhD
Mellen Center, Cleveland Clinic, Cleveland, OH; Associate Professor of Neurology, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Mary R. Rensel, MD
Mellen Center, Cleveland Clinic, Cleveland, OH; Assistant Professor of Neurology, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Jeffrey A. Cohen, MD
Mellen Center, Cleveland Clinic, Cleveland, OH; Professor of Neurology, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Amy Kunchok, MD
Mellen Center, Cleveland Clinic, Clevland, OH; Clinical Assistant Professor of Neurology, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Reproductive issues and multiple sclerosis: 20 questions

ABSTRACT

Multiple sclerosis (MS) is commonly diagnosed in young adults during their reproductive years. Consequently, concerns about family planning and MS management related to pregnancy and breastfeeding are often encountered in clinical practice. Pregnancy itself is not harmful for women with MS. However, disease-modifying therapies (DMTs) have implications for reproductive planning, including stopping treatment while trying to conceive and during pregnancy, as well as managing fetal risks. People with MS and their care team must engage in collaborative decision-making before, during, and after pregnancy. Based on the results of a consensus-building initiative, answers are provided to 20 frequently asked questions regarding the management of MS during pregnancy planning, pregnancy, and the postpartum period.

KEY POINTS

Most women with MS can conceive, have normal pregnancies and deliveries, and breastfeed successfully.

Primary considerations relate to ensuring proper prenatal counseling about cessation of DMT and timing of conception, as well as resumption of DMT.

To engage in collaborative decision-making throughout all stages of pregnancy, clinicians caring for people with MS need to be familiar with pregnancy-related risks associated with MS therapies, as well as the management of MS-related reproductive issues.

doi:10.3949/ccjm.90a.22066

Multiple sclerosis (MS), a chronic, inflammatory, neurodegenerative disease, is often diagnosed during patients' childbearing years. As a result, family planning, contraception, pregnancy, and childbirth are significant concerns. Healthcare for people with MS requires access to information and clinicians who can provide guidance. MS itself is not a barrier to pregnancy, but disease-modifying therapies (DMTs) for MS are associated with varying degrees of risks to the fetus. Many risks are theoretical due to limited fetal safety data, but they require careful consideration by both clinician and patient.

Clinicians at the Cleveland Clinic Mellen Center for Multiple Sclerosis developed a collaborative approach to reproductive health and MS, a summary of which is available on the Mellen Center website.[1] This article, based on the Mellen Center consensus initiative, combines a review of the literature with clinical experience to address 20 frequently asked questions about the management of MS during family planning, pregnancy, and the postpartum period.

1: DOES MS IMPACT SEXUAL HEALTH AND FERTILITY?

Sexual dysfunction affects 40% to 80% of women and 50% to 90% of men who have MS,[2] imposing a significant negative impact on quality of life. Targeted symptomatic therapies such as lubricants, sex steroid therapy, prostaglandins, phosphodiesterase 5 inhibitors, or psychotherapy may be utilized. When symptomatic therapies are unsuccessful,

patients may benefit from further evaluation through gynecologic or urologic specialists.[3]

Conception and fertility rates in people with MS and the general population are comparable. The use of assisted reproductive technology has been reported in some studies to be associated with an increased risk of MS relapse in the first 3 months following unsuccessful cycles.[4] However, a recently published study did not identify this risk.[5]

2: WHAT IS THE GENETIC RISK OF MS IN CHILDREN OF PEOPLE WITH MS?

Children of people with MS are approximately 5.77 times more likely to develop MS than people in the general population,[6] though the overall risk remains low at approximately 2%.[7] Although genetic factors contribute to susceptibility to MS, the disorder is complex, with more than 250 identified contributory genes. The development of MS likely also depends on environmental and other factors including exposure to smoking, viral infections, adolescent obesity, vitamin D levels, microbiome, and geographic latitude of residence.[8]

3: WHAT ARE THE KEY ISSUES FOR CHOICE OF DMT IN PRECONCEPTION COUNSELING?

The choice of DMT should be based on the patient's level of disease activity, their plans to become pregnant, and the desired timing. Most DMTs are associated with fetal risk; further, the sphingosine 1-phosphate receptor (S1Pr) modulators and natalizumab are associated with a risk of rebound disease activity upon discontinuation.

4: WHAT ARE THE RECOMMENDATIONS FOR CONTRACEPTION?

Women with MS of childbearing potential who are using DMT should practice effective birth control regardless of plans to pursue pregnancy. In general, contraceptive methods used in the population at large are safe and effective for women with MS. Potential drug-drug interactions between symptomatic treatments (for MS-related sequelae such as spasticity, urinary dysfunction, and mood dysregulation) and certain contraceptive agents should be considered: for example, modafinil may lessen the efficacy of oral contraceptives by accelerating their metabolism.

Men with MS treated with teriflunomide, which carries significant risk of teratogenicity, must practice effective contraception until after the medication is cleared by metabolism (ie, at least 6 months after the last dose) or by a rapid-clearance protocol. Female partners of men taking teriflunomide must also be counseled on the potential risks of fetal exposure and use of effective contraceptive therapy. Teriflunomide is contraindicated for use during pregnancy and in females of reproductive age not using effective contraception.

Cladribine has been associated with increased embryo lethality in animal studies, and men are thus advised to prevent pregnancy for at least 6 months following treatment with cladribine.[9] Cladribine may cause an increase in nonmotile sperm, leading to reversible infertility.[10]

Alemtuzumab may cause reversible infertility by inactivating mature sperm by binding to CD52, the surface antigen expressed by mature sperm.[11]

5: ARE THERE SPECIFIC CARE REQUIREMENTS DURING PREGNANCY?

MS itself does not render a pregnancy "high-risk" or increase the likelihood of congenital malformation or miscarriage. MS may be associated with lower birthweight,[4] although this is usually not clinically significant.

The overall risk of MS relapse decreases during pregnancy, with the relapse rate declining progressively over the 3 trimesters.[12] The patient's recent disease trajectory and her prior DMT pharmacology, efficacy, and latency may influence disease activity during pregnancy. Women with higher relapse rates prior to conception are at increased risk of ongoing disease activity during pregnancy.[12]

6: IS IT SAFE TO USE DMT DURING PREGNANCY?

The use of DMT is generally not recommended during pregnancy. Treatment considerations must include the potential benefits and risks to the mother based on her level of disease activity and the likelihood of relapse or worsening disability without DMT. Embryonic or fetal exposure is also associated with risk (**Table 1**).[1,5,10,11,13–41]

Platform injectable therapies

The first DMTs—the "platform therapies," ie, interferons[13–17] and glatiramer acetate[18,19]—have been associated with low birth weight but not with other significant adverse effects on pregnancy. These treatments are generally stopped before planned conception. However, when benefits outweigh risks, they may be continued in women with MS who are pregnant or wish to become pregnant and whose risk profile is low.

TABLE 1
Special considerations for use of disease-modifying therapies in pregnancy[a,b]

Medication	Recommended washout period	Use in pregnancy
Interferons Interferon beta-1a[14,15] Peginterferon beta-1a[16] Interferon beta-1b[13,17]	2 weeks	Use only if benefit outweighs risks
Glatiramer acetate[18,19]	None	Use only if benefit outweighs risks
Fumarates Dimethyl fumarate[28] Diroximel fumarate[29] Monomethyl fumarate[30]	1 week	Not advised
Sphingosine 1-phosphate receptor modulators Fingolimod[32] Siponimod[33] Ozanimod[34] Ponesimod[35]	Fingolimod: 2–3 months Siponimod: 2 weeks Ozanimod: 3 months Ponesimod: 1 week	Spingosine 1-phosphate receptor modulators are not advised Risk for rebound disease activity Consider transition to a B-cell-depleting agent before discontinuing contraception
Cladribine[10]	6 months	Not advised
Teriflunomide[31]	Rapid-elimination procedure required: cholestyramine 8 g every 8 hours orally for 11 days (if not tolerated, reduce dose to 4 g every 8 hours) or activated charcoal powder 50 g every 12 hours for 11 days until a serum concentration below 0.02 mg/L is reached	Not advised; stop treatment and eliminate drug before discontinuing contraception
Natalizumab[21]	2–3 months	Generally not advised Use in special circumstances; high risk for rebound disease activity Consider transition to a B-cell-depleting agent before discontinuing contraception
B-cell–depleting agents Ocrelizumab[22] Ofatumumab[23] Rituximab[24,25] Ublituximab[26]	1–3 months[c]	B-cell–depleting agents are generally not advised; package inserts recommend washout periods of 6 months for ocrelizumab, 6 months for ofatumumab, 6 months for ublituximab, and 12 months for rituximab[c]
Alemtuzumab[27]	4 months	Use not advised

[a] This table reflects our clinical practice and review of combined recommendations of prescribing information and key articles.
[b] Pregnancy testing is recommended before starting or re-dosing for all disease-modifying therapy in women of childbearing potential.
[c] See Question 7 in the article for an in-depth discussion of B-cell-depleting therapies and pregnancy timing.

Based on information in references 1,5,10,11, and 13–41.

Monoclonal antibodies

With few exceptions, the use of monoclonal antibodies during pregnancy is not advised. Placental transfer of immunoglobulins begins around the second trimester and increases with gestational age, theoretically lowering the risk of fetal exposure in the first trimester.[20] Natalizumab may be considered during pregnancy in exceptional circumstances, as in women with severe intrapartum relapses.[12] Its use during the third trimester requires caution because of risk of placental transfer and resulting fetal or infantile pancytopenia.[21] B-cell–depleting therapies

(ocrelizumab, ofatumumab, rituximab, ublituximab)[22–26] can be used prior to pregnancy, but their routine administration is not recommended during pregnancy. Use of alemtuzumab during pregnancy is not advised.[27]

Oral therapies

None of the currently available oral therapies—fumarates,[28–30] teriflunomide,[31] S1Pr modulators,[32–35] or cladribine[10]—are safe for use during pregnancy.

7: HOW LONG BEFORE CONCEPTION SHOULD DMT BE STOPPED?

Washout periods are advised for all DMTs, with consideration of the pharmacokinetics of each medication and the patient's level of disease activity. The pharmacology of the treatment determines recommended minimum washout periods (**Table 1**). When feasible, the timing of treatment and conception should be coordinated with the aim of keeping DMT washout periods as short as possible to mitigate risk of MS relapse.

Prescribing information approved by the US Food and Drug Administration (FDA) recommends that women continue contraception for 6 months following the last treatment of ocrelizumab,[22] ofatumumab,[23] and ublituximab,[26] and for 12 months following the last treatment of rituximab.[24,25] A pregnancy test should be conducted prior to subsequent dosing of intravenous B-cell–depleting therapies. Ofatumumab is administered by monthly subcutaneous injection, and the FDA-approved prescribing information recommends contraception for 6 months following the last treatment.[23] Ofatumumab is thought to protect against disease activity for 6 to 9 months.[23]

B-cell–depleting therapies infused intravenously may confer prolonged protective effects against MS relapses for 6 to 9 months after administration. Decisions regarding use of B-cell–depleting therapy and pregnancy planning need to consider the patient's degree of disease activity, risks, and individual preferences. When disease is highly active before initiation of B-cell–depleting therapy and it is necessary to minimize time off DMT, the patient may receive a B-cell–depleting therapy and then attempt pregnancy after 1 to 3 months.[36,42,43] The rationale is that based on half-life, these therapies are eliminated 3.5 to 4.5 months after an infusion.[22,24,25] Placental transfer of immunoglobulin G is minimal in the first trimester,[20] so the risk of fetal exposure in the second trimester is low if conception occurs 3 to 6 months after the last dose of B-cell–depleting therapy.[36]

8: CAN DISEASE ACTIVITY RETURN WHEN DMT IS PAUSED FOR PREGNANCY?

Women treated with S1Pr modulators or natalizumab prior to conception may have increased risk for rebound disease after medication withdrawal. Annualized MS relapse rates have been shown to be higher throughout pregnancy after fingolimod and natalizumab discontinuation compared with low-efficacy therapies.[12] In women discontinuing natalizumab, relapses during pregnancy and the postpartum year have been reported in up to 67% of patients.[37] Due to the risk of rebound disease activity in people with MS treated with these medications, changing to an alternate therapy such as a B-cell–depleting agent might be considered before discontinuing contraception, especially in women with highly active disease.[44]

9: WHAT IS THE NEXT STEP IF PREGNANCY OCCURS WHILE THE PATIENT IS TAKING A DMT?

If a woman becomes pregnant while taking DMT, the therapy should be discontinued and the pregnancy exposure reported through an appropriate MS pregnancy registry (**Table 2**).[1,5,10,11,13–41] Follow-up after discontinuation of therapy varies depending on the DMT as follows:

- **Interferon beta or glatiramer acetate:** no additional monitoring required during pregnancy
- **Oral therapies:** referral for early ultrasonography to screen for major malformations
- **Teriflunomide:** rapid-elimination procedure initiated as soon as possible (**Table 1**) and referral to an obstetrician with expertise in high-risk pregnancies for early ultrasonography to screen for major malformations
- **Cladribine, teriflunomide, or natalizumab:** follow-up with an obstetrician with expertise in high-risk pregnancies.

10: HOW ARE RELAPSES MANAGED DURING PREGNANCY?

The patient's obstetrician and neurologist should coordinate management of MS relapses during pregnancy. Mild relapses with nondisabling symptoms or spontaneous improvement might require no intervention. If a relapse warrants intervention, the typical treatment is high-dose corticosteroids, usually intravenous methylprednisolone 1 g daily or oral prednisone 1,250 mg daily for 3 to 5 days. This therapy carries a slightly increased risk for adverse fetal

TABLE 2
Risks and management recommendations: Fetal exposure to disease-modifying therapies[a]

Medication	First-trimester exposure recommendations	Exposure risks
Interferons Interferon beta-1a[14,15] Peginterferon beta-1a[16] Interferon beta-1b[13,17]	No additional fetal or neonatal monitoring	With interferons, slight risk of decreased birthweight and increased embryo or fetal death based on animal data
Glatiramer acetate[18,19]	No additional fetal or neonatal monitoring	None
Fumarates Dimethyl fumarate[28] Diroximel fumarate[29] Monomethyl fumarate[30]	Early ultrasonography for major malformations	Dimethyl fumarate: uncertain risk to fetus; animal studies have shown low birthweight, delayed development, delayed ossification, spontaneous abortions, decreased fetal viability, and impaired learning and memory Diroximel fumarate: based on animal data, may cause fetal harm including skeletal abnormalities, increased mortality, decreased body weight, and neurobehavioral impairment Monomethyl fumarate: Based on animal data, may cause fetal harm including adverse embryotoxicity, reduction in body weight, and delayed sexual maturation
S1Pr modulators Fingolimod[32] Siponimod[33] Ozanimod[34] Ponesimod[35]	Early ultrasonography for major malformations	All: teratogenic effect likely; risk of neural tube defects, fetal loss and fetal abnormalities Fingolimod: based on animal studies, increased risk of congenital malformations and embyrolethality, fetal growth retardation, and neurobehavioral deficits Siponimod: based on animal studies, increased risk of congenital malformations and embyrolethality, increased incidence of skeletal variations, decreased body weight, and delayed sexual maturation Ozanimod: based on animal studies, increased risk of congenital malformations and embyrolethality, skeletal variations, vascular malformations, and neurobehavioral deficits Ponesimod: based on animal studies, increased risk of congenital malformations and embyrolethality, visceral , cardiac, and skeletal malformations
Cladribine[10]	Follow up with high-risk obstetrician	Risk of congenital malformations and embyrolethality based on animal studies
Teriflunomide[31]	Early screening for major and minor malformations; option to follow up with high-risk obstetrician	Highly teratogenic; risk of serious birth defects in fetus; risk of preterm labor; risk of low birthweight
Natalizumab[21]	Screen neonate for liver dysfunction, pancytopenia	Risk of mild to moderate hematologic alterations (pancytopenia with late pregnancy exposure)
B-cell–depleting agents Ocrelizumab[22] Ofatumumab[23] Rituximab[24,25] Ublituximab[26]	Screen neonate for B-cell depletion, pancytopenia	With B-cell–depleting agents, there is a risk of B-cell depletion in fetus or infant with second-trimester and third-trimester exposure Rituximab: risk of congenital malformations in fetus, and neonatal infections
Alemtuzumab[27]	Monitor thyroid studies	Risk of thyroid disease in mother (autoimmune thyroiditis in up to 40%); risk of low birthweight, preterm birth, preeclampsia; risk of neonatal Graves disease and cognitive impairment

[a]This table reflects our clinical practice and review of combined recommendations of prescribing information and key articles.

S1Pr = sphingosine 1-phosphate receptor

Based on information in references 1,5,10,11, and 13–41.

outcomes such as cleft palate and low birth weight.[36] Maternal risks include hyperglycemia, hypertension, and fluid overload.

Corticosteroid use should be avoided during the first trimester when possible. If the patient develops a disabling steroid-refractory relapse, then intravenous immunoglobulin therapy[45] or plasmapheresis may be considered. The increased thrombotic risk with intravenous immunoglobulin should be taken into consideration. Nonpharmacologic interventions such as physical therapy can be utilized when deemed appropriate by the patient's care team.

11: IS MAGNETIC RESONANCE IMAGING SAFE DURING PREGNANCY?

Despite there being no absolute contraindications to magnetic resonance imaging (MRI) during pregnancy, it is generally avoided. It can be done if clinically indicated, as when findings are critical to clinical decision-making and are expected to impact outcomes. Gadolinium-based contrast should be used with caution, as studies have demonstrated increased risk of stillbirth, neonatal death, and various inflammatory conditions.[46]

12: ARE VACCINATIONS SAFE DURING PREGNANCY?

Barring contraindications, the vaccination schedule for the general population is applicable to people with MS.[47] Vaccination updates are best before starting DMT. Any live attenuated vaccines that need to be updated may be administered following delivery and before restarting DMT.

13: ARE THERE SPECIFIC REQUIREMENTS FOR LABOR AND DELIVERY?

For most women, there are no MS-specific recommendations for childbirth. Many women can have spontaneous-onset labor and full-term vaginal delivery. Individual factors may need to be considered for women with significant disability, such as planning for assisted delivery methods or cesarean delivery in women with significant motor disability, increased risk of deep vein thrombosis in nonambulatory patients, and increased risk of urinary tract infection in women requiring self-catheterization. The use of any anesthetic is acceptable when clinically indicated,[48] including regional anesthesia as with epidural injections.

14: ARE THERE SPECIFIC POSTPARTUM REQUIREMENTS?

Neurologic care generally should resume 4 to 6 weeks postpartum. At that time, breastfeeding plans should be confirmed or revised and resumption of DMT arranged. Women with MS should receive routine obstetric postpartum care, and duration of birth hospitalizations are in the normal range.[49] Patients should be screened for depression and anxiety at follow-up visits. The risk of perinatal depression is higher than in the general population, although the prognosis for recovery at 18 months is similar.[50]

15: WHAT IS THE RISK OF RELAPSE AFTER DELIVERY?

Women with MS may be at risk for return of disease activity in the postpartum period. Higher relapse rates before pregnancy are associated with higher postpartum relapse rates. Approximately 13% of women with term or preterm deliveries experience a clinical relapse within 3 months of delivery.[12]

16: WHEN SHOULD DMT BE RESUMED?

Breastfeeding plans and timing of DMT resumption should be discussed prior to delivery. When to resume DMT is an individual decision that needs to account for previous disease activity and breastfeeding plans. Resumption of DMT early postpartum should be considered for women with highly active disease before conception or relapse during pregnancy. Women with a low level of disease activity may reasonably defer DMT resumption while they are breastfeeding.

17: IS BREASTFEEDING SAFE WITH DMT?

Data are limited concerning the safety of DMT for the breastfed infant, so use of DMT during breastfeeding is generally not advised. The decision to breastfeed and its duration should balance its benefits with the risk of relapse. Notably, the decision to breastfeed requires a delay in DMT resumption that may increase the risk of relapse. The patient's disease characteristics must be considered.

Most DMTs are considered unsafe for use during breastfeeding. The exception is glatiramer acetate, recently approved by European Union health authorities for use during breastfeeding[38] based on the rationale that benefits of breastfeeding likely exceed the risk of exposure.

The degree of transfer of DMTs into breast milk

depends on the size of the molecule. Interferon beta are larger than 20kDa, and glatiramer acetate molecules are 5 to 9 kDa, and the amount of transfer to breast milk is low.[51] B-cell–depleting therapies involve much larger molecules, on the scale of 145 kDa, and their low oral bioavailability limits absorption by the newborn; the relative infant dose is less than 10%.[39] Even so, B-cell–depleting therapies may have clinical implications for the infant such as B-cell depletion and impaired vaccine responses, though this concern remains theoretical.

Natalizumab is detectable in breast milk in small amounts and therefore should also be used with caution.[51] Dimethyl fumarate, S1Pr modulators, cladribine, alemtuzumab, and teriflunomide should not be used during breastfeeding given their risk profiles (**Table 2**).[36,40]

18: HOW SHOULD A RELAPSE BE MANAGED WHILE A PATIENT IS BREASTFEEDING?

Relapses of MS that occur during breastfeeding can be treated as they usually would be. Transfer of methylprednisolone through breastmilk is thought to be minimal and may be further minimized by delaying breastfeeding for 2 to 4 hours after treatment: levels peak approximately 2 hours after infusion and decline rapidly thereafter, falling below the limits of detection 24 hours after infusion.[52,53] For women receiving oral prednisone, the dose ingested by the infant through breastmilk is thought to be negligible, and no adverse effects have been reported in infants breastfed by mothers in general receiving oral corticosteroid treatment.[41]

19: IS MRI SAFE DURING BREASTFEEDING?

Gadolinium contrast for MRI studies may be used while breastfeeding when clinically necessary: although small amounts are detectable in breastmilk, there is little gastrointestinal absorption.[54] If there is any concern for potential toxicity, the patient may refrain from breastfeeding or discard breastmilk for 12 to 24 hours after contrast administration.

20: WHAT ARE THE SPECIFIC PREGNANCY AND FERTILITY ISSUES WITH AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANT?

Infertility is common in both men and women after autologous hematopoietic stem cell transplant, and gonadal toxicity results from the cytotoxic therapies that comprise the mobilization and conditioning regimens.[55] Therefore, pretreatment counseling regarding the risk of infertility is critical. People with MS may wish to consider fertility preservation such as cryopreservation of sperm, mature oocytes, or fertilized embryos, and referral to an oncofertility specialist may be appropriate. Limited data suggest that infants born to women who have undergone autologous hematopoietic stem cell transplant do not have an increased risk of congenital abnormalities.[55]

TAKE-HOME MESSAGES

Management of MS is complex and requires individualized treatment, and pregnancy and reproductive issues are often at the forefront of concerns for both women and men of reproductive age. The individual's care team, including the primary care clinician, internist, obstetrician, and neurologist, need to engage in collaborative decision-making before, during, and after pregnancy to optimize the management of MS-related reproductive issues. ■

DISCLOSURES

Dr. Carlson discloses fellowship funding (Grant 16696-P-FEL) from Biogen and institutional clinical training award (ICT-1805-31154) from National MS Society. Dr. Ontaneda discloses consulting for Biogen Idec; consulting and research for Genentech; and consulting for Novartis. Dr. Rensel discloses consulting, teaching and speaking, and research for Biogen Idec; private ownership/partnership of Brain Fresh LLC; consulting and independent contracting for Bristol-Myers Squibb; teaching and speaking and research for Genentech/Roche; work as advisor or research panel participant and teaching and speaking for Genzyme; work as advisor or research panel participant for National MS Society; teaching and speaking for Novartis; and work as advisor or research panel participant for EMD Serono. Dr. Cohen discloses consulting for Biogen, Bristol-Myers Squibb, Convelo, EMD Serono, GlaxoSmithKline, Janssen Pharmaceuticals, Mylan Pharma, PSI Pharma Support America; and work as editor for Sage Publishing. Dr. Kunchok discloses consulting for EMD Serono; work as advisor or review panel participant for Genentech and Horizon Therapeutics; and work as editor for the journal *Neurology*.

REFERENCES

1. **Cleveland Clinic Mellen Center for Multiple Sclerosis.** Mellen Center approach: management of multiple sclerosis during pregnancy. Updated October 14, 2021. https://my.clevelandclinic.org/-/scassets/files/org/neurological/mellen-center/management-of-multiple-sclerosis-during-pregnancy.pdf. Accessed March 13, 2023.
2. **Drulovic J, Kisic-Tepavcevic D, Pekmezovic T.** Epidemiology, diagnosis and management of sexual dysfunction in multiple sclerosis. Acta Neurol Belg 2020; 120(4):791–797. doi:10.1007/s13760-020-01323-4
3. **Guo ZN, He SY, Zhang HL, Wu J, Yang Y.** Multiple sclerosis and sexual dysfunction. Asian J Androl 2012; 14(4):530–535. doi:10.1038/aja.2011.110
4. **Hellwig K.** Pregnancy in multiple sclerosis. Eur Neurol 2014; 72(suppl 1):39–42. doi:10.1159/000367640
5. **Mainguy M, Tillaut H, Degremont A, et al.** Assessing the risk

of relapse requiring corticosteroids after in vitro fertilization in women with multiple sclerosis. Neurology 2022; 10.1212/WNL.0000000000201027. doi:10.1212/WNL.0000000000201027
6. **Westerlind H, Ramanujam R, Uvehag D, et al.** Modest familial risks for multiple sclerosis: a registry-based study of the population of Sweden. Brain 2014; 137(Pt 3):770–778. doi:10.1093/brain/awt356
7. **Balcerac A, Louapre C.** Genetics and familial distribution of multiple sclerosis: A review. Rev Neurol (Paris). 2022; 178(6):512–520. doi:10.1016/j.neurol.2021.11.009
8. **Simpson S Jr, Blizzard L, Otahal P, Van der Mei I, Taylor B.** Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. J Neurol Neurosurg Psychiatry 2011; 82(10):1132–1141. doi:10.1136/jnnp.2011.240432
9. **Cook S, Vermersch P, Comi G, et al.** Safety and tolerability of cladribine tablets in multiple sclerosis: the CLARITY (CLAdRIbine Tablets treating multiple sclerosis orallY) study. Mult Scler 2011; 17(5):578–593. doi:10.1177/1352458510391344
10. **EMD Serono, Inc.** Mavenclad (Cladribine) package insert. https://www.emdserono.com/us-en/pi/mavenclad-pi.pdf. Accessed March 13, 2023.
11. **Cree BA.** Update on reproductive safety of current and emerging disease-modifying therapies for multiple sclerosis. Mult Scler 2013; 19(7):835–843. doi:10.1177/1352458512471880
12. **Yeh WZ, Widyastuti PA, Van der Walt A, et al.** Natalizumab, fingolimod and dimethyl fumarate use and pregnancy-related relapse and disability in women with multiple sclerosis. Neurology 2021; 96(24):e2989–e3002. doi:10.1212/WNL.0000000000012084
13. **Bayer HealthCare Pharmaceuticals, Inc.** Betaseron (interferon-1b) package insert. https://labeling.bayerhealthcare.com/html/products/pi/Betaseron_PI.pdf. Accessed March 13, 2023.
14. **Biogen, Inc.** Avonex (interferon beta-1a) package insert. https://www.avonex.com/content/dam/commercial/avonex/pat/en_us/pdf/Avonex_US_Prescribing_Information.pdf. Accessed March 13, 2023.
15. **EMD Serono, Inc.** Rebif (interferon beta-1a) package insert. https://www.emdserono.com/us-en/pi/rebif-pi.pdf. Accessed March 13, 2023.
16. **Biogen, Inc.** Plegridy (peginterferon beta-1a) package insert. https://www.plegridy.com/content/dam/commercial/plegridy/pat/en_us/pdf/plegridy-prescribing-information.pdf. Accessed March 13, 2023.
17. **Novartis Pharmaceuticals Corp.** Extavia (interferon-1b) package insert. https://www.novartis.com/us-en/sites/novartis_us/files/extavia.pdf. Accessed March 13, 2023.
18. **Teva Neuroscience, Inc.** Copaxone (glatiramer acetate) package insert. https://www.copaxone.com/globalassets/copaxone/prescribing-information.pdf. Accessed March 13, 2023.
19. **Sandoz, Inc.** Glatopa (glatiramer acetate) package insert. https://www.glatopa.com/globalassets/glatopa-com/pdf/glatopa20_40_pi_2018.pdf. Accessed March 13, 2023.
20. **DeSesso JM, Williams AL, Ahuja A, Bowman CJ, Hurtt ME.** The placenta, transfer of immunoglobulins, and safety assessment of biopharmaceuticals in pregnancy. Crit Rev Toxicol 2012; 42(3):185–210. doi:10.3109/10408444.2011.653487
21. **Biogen, Inc.** Tysabri (natalizumab) package insert. https://www.tysabri.com/content/dam/commercial/tysabri/pat/en_us/pdf/tysabri_prescribing_information.pdf. Accessed March 13, 2023.
22. **Genentech, Inc.** Ocrevus (ocrelizumab) package insert. https://www.gene.com/download/pdf/ocrevus_prescribing.pdf. Accessed March 13, 2023.
23. **Novartis Pharmaceuticals Corp.** Kesimpta (ofatumumab) package insert. https://www.novartis.com/us-en/sites/novartis_us/files/kesimpta.pdf. Accessed March 13, 2023.
24. **Genentech, Inc.** Rituxan (rituximab) package insert. https://www.gene.com/download/pdf/rituxan_prescribing.pdf. Accessed March 13, 2023.
25. **Pfizer.** Ruxience (rituximab-pvrr) package insert. https://labeling.pfizer.com/ShowLabeling.aspx?id=12090. Accessed March 8, 2023.
26. **TG Therapeutics.** Briumvi (ublituximab-xiiy) package insert. https://www.tgtherapeutics.com/label-prescribing-info/uspi-briumvi.pdf. Accessed March 13, 2023.
27. **Genzyme Corp.** Lemtrada (alemtuzumab) package insert. https://products.sanofi.us/lemtrada/lemtrada.pdf. Accessed March 8, 2023.
28. **Biogen, Inc.** Tecfidera (dimethyl fumarate) package insert. https://www.tecfidera.com/content/dam/commercial/tecfidera/pat/en_us/pdf/full-prescribing-info.pdf. Accessed March 13, 2023.
29. **Biogen, Inc.** Vumerity (diroximel fumarate) package insert. https://www.vumerity.com/content/dam/commercial/vumerity/pat/en_us/pdf/vumerity-prescribing-information.pdf. Accessed March 13, 2023.
30. **Banner Life Sciences, LLC.** Bafiertam (monomethyl fumarate) package insert. https://www.bafiertam.com/pdf/bafiertam-prescribing-information.pdf. Accessed March 13, 2023.
31. **Genzyme Corp.** Aubagio (teriflunomide) package insert. https://products.sanofi.us/aubagio/aubagio.pdf. Accessed March 13, 2023.
32. **Novartis Pharmaceuticals Corp.** Gilenya (fingolimod) package insert https://www.novartis.com/us-en/sites/novartis_us/files/gilenya.pdf. Accessed March 13, 2023.
33. **Novartis Pharmaceuticals Corp.** Mayzent (siponimod) package insert. https://www.novartis.com/us-en/sites/novartis_us/files/mayzent.pdf. Accessed March 13, 2023.
34. **Bristol Meyers Squibb.** Zeposia (ozanimod) package insert. https://packageinserts.bms.com/pi/pi_zeposia.pdf. Accessed March 13, 2023.
35. **Janssen Pharmaceuticals, Inc.** Ponvory (ponesimod) package insert. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/PONVORY-pi.pdf. Accessed March 13, 2023.
36. **Langer-Gould AM.** Pregnancy and family planning in multiple sclerosis. Continuum (Minneap Minn) 2019; 25(3):773–792. doi:10.1212/CON.0000000000000745
37. **Hellwig K, Tokic M, Thiel S, et al.** Multiple sclerosis disease activity and disability following discontinuation of natalizumab for pregnancy. JAMA Netw Open 2022; 5(1):e2144750. doi:10.1001/jamanetworkopen.2021.44750
38. **Ciplea AI, Kurzeja A, Thiel S, et al.** Eighteen-month safety analysis of offspring breastfed by mothers receiving glatiramer acetate therapy for relapsing multiple sclerosis—COBRA study. Mult Scler 2022; 28(10):1641–1650. doi:10.1177/13524585221083982
39. **Bove RM, Houtchens MK.** Pregnancy management in multiple sclerosis and other demyelinating diseases. Continuum (Minneap Minn) 2022; 28(1):12–33. doi:10.1212/CON.0000000000001108
40. **Krysko KM, LaHue SC, Anderson A, et al.** Minimal breast milk transfer of rituximab, a monoclonal antibody used in neurological conditions. Neurol Neuroimmunol Neuroinflamm 2019; 7(1):e637. doi:10.1212/NXI.0000000000000637
41. **National Library of Medicine.** Prednisone. In: Drugs and Lactation Database (LactMed). Bethesda, MD: National Library of Medicine; 2021.
42. **Langer-Gould A, Smith J, Albers K, et al.** Pregnancy-related relapses in a large, contemporary multiple sclerosis cohort: no increased risk in the postpartum period. Presented at: American Academy of Neurology Annual Meeting; May 4–9, 2019; Philadelphia, PA.
43. **Krysko KM, Bove R, Dobson R, Jokubaitis V, Hellwig K.** Treatment of women with multiple sclerosis planning pregnancy. Curr Treat Options Neurol 2021; 23(4):11. doi:10.1007/s11940-021-00666-4
44. **Alping P, Frisell T, Novakova L, et al.** Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. Ann Neurol 2016; 79(6):950–958. doi:10.1002/ana.24651
45. **Winkelmann A, Rommer PS, Hecker M, Zettl UK.** Intravenous immunoglobulin treatment in multiple sclerosis: a prospective, rater-blinded analysis of relapse rates during pregnancy and the postnatal period. CNS Neurosci Ther 2019; 25(1):78–85. doi:10.1111/cns.12985
46. **Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL.** Association between MRI exposure during pregnancy and fetal and childhood outcomes. JAMA 2016; 316(9):952–961. doi:10.1001/jama.2016.12126
47. **US Centers for Disease Control and Prevention.** Guidelines for vaccinating pregnant women. Updated July 13, 2022. https://www.cdc.gov/vaccines/pregnancy/hcp-toolkit/guidelines.html. Accessed March 13, 2023.
48. **Pastò L, Portaccio E, Ghezzi A, et al.** Epidural analgesia and cesarean delivery in multiple sclerosis post-partum relapses: the Italian co-

hort study. BMC Neurol 2012; 12:165. doi:10.1186/1471-2377-12-165
49. **Lu E, Zhao Y, Dahlgren L, et al.** Obstetrical epidural and spinal anesthesia in multiple sclerosis. J Neurol 2013; 260(10):2620–2628. doi:10.1007/s00415-013-7035-7
50. **Eid K, Torkildsen ØF, Aarseth J, et al.** Perinatal depression and anxiety in women with multiple sclerosis: a population-based cohort study. Neurology 2021; 96(23):e2789–e2800. doi:10.1212/WNL.0000000000012062
51. **Fragoso YD, Adoni T, Alves-Leon SV, et al.** Postpartum treatment with immunoglobulin does not prevent relapses of multiple sclerosis in the mother. Health Care Women Int 2015; 36(10):1072–1080. doi:10.1080/07399332.2014.948627
52. **Boz C, Terzi M, Zengin Karahan S, Sen S, Sarac Y, Emrah Mavis M.** Safety of IV pulse methylprednisolone therapy during breastfeeding in patients with multiple sclerosis. Mult Scler 2018; 24(9): 1205–1211. doi:10.1177/1352458517717806
53. **Zengin Karahan S, Boz C, Terzi M, et al.** Methylprednisolone concentrations in breast milk and serum of patients with multiple sclerosis treated with IV pulse methylprednisolone. Clin Neurol Neurosurg 2020; 197:106118. doi:10.1016/j.clineuro.2020.106118
54. **ACR Committee on Drugs and Contrast Media.** ACR Manual on Contrast Media: 2022. https://www.acr.org/-/media/ACR/files/clinical-resources/contrast_media.pdf. Accessed March 13, 2023.
55. **Tichelli A, Rovó A.** Fertility issues following hematopoietic stem cell transplantation. Expert Rev Hematol 2013; 6(4):375–388. doi:10.1586/17474086.2013.816507

Address: *Amy Kunchok, MD, Mellen Center, U10, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; kunchoa@ccf.org*

Join Our Team

Growth. Advancement. Opportunity.

These are just a few reasons to join our team of physicians and advance practice providers at Cleveland Clinic in Ohio, Florida, Nevada, Abu Dhabi and London. As a physician-led organization, we base our culture on collaboration and Patients First. Because we push the boundaries of performance, we offer competitive compensation and benefits that equal or surpass our peer organizations.

To learn more and view our physician staff and advanced practice listings, please visit jobs.clevelandclinic.org.

Cleveland Clinic is pleased to be an equal employment/ affirmative action employer: Women/Minorities/Veterans/ Individuals with Disabilities. Smoke/drug free environment.

Cleveland Clinic

Every life deserves world class care.

Mary M. Volcheck, MSN, RN
Department of Nursing, Mayo Clinic, Rochester, MN

Stephanie M. Graham, RN
Department of Nursing, Mayo Clinic, Rochester, MN

Kevin C. Fleming, MD
Division of General Internal Medicine, Mayo Clinic, Rochester, MN

Arya B. Mohabbat, MD
Division of General Internal Medicine, Mayo Clinic, Rochester, MN

Connie A. Luedtke, RN, PMGT-BC
Department of Nursing, Mayo Clinic, Rochester, MN

Central sensitization, chronic pain, and other symptoms: Better understanding, better management

ABSTRACT

Central sensitization, a pathophysiologic process in which the central nervous system undergoes changes that alter its processing of pain and other sensory stimuli, may be the mechanism underlying various conditions in which patients have unexplained pain and fatigue. Patients frequently misunderstand the cause of their symptoms and pursue unnecessary evaluations and treatments. Clinicians have a pivotal role in decreasing this misunderstanding by providing patient education, which can affect perception, management, functional status, and quality of life.

KEY POINTS

In central sensitization, the central nervous system undergoes structural, functional, and chemical changes that make it more sensitive to pain and other sensory stimuli.

Central sensitization provides an explanatory framework for various frequently encountered conditions.

Patient education about pain physiology and central sensitization can improve quality of life and functional status, and reduce anxiety and catastrophization.

Cognitive behavior therapy aims to reframe negative thoughts, emotions, and behaviors as positive ones.

doi:10.3949/ccjm.90a.22019

When patients have chronic pain or other symptoms that seem out of proportion to anything we can tell is physically wrong with them, we should not assume they are faking it. The central nervous system can undergo changes—structural, functional, and chemical—that make it more sensitive to stimuli, a process called *central sensitization*.[1]

The concept has everyday relevance. In 2016, an estimated 20% of Americans had chronic pain that markedly worsened their life and raised their healthcare costs.[2] In fact, chronic pain can adversely affect every aspect of a person's life—physical, emotional, social, and financial.

Many patients with chronic pain pursue lengthy rounds of medical appointments and tests and seek relief through prescription medications, including opioids. Opioid-associated deaths have reached epidemic numbers. In the United States alone, opioid overdoses are estimated to cause 115 deaths every day,[3] and in 2020, overdoses of all types of drugs killed more than 93,000 people, an increase of more than 28% from the previous year.[4] Although it is impossible to know for certain, we hypothesize that many of these deaths were associated with chronic pain.[5]

However, it is possible—and imperative—to help shift a patient's attention away from potentially harmful treatments and toward effective nonpharmacologic methods of pain management. Educating patients about the physiology of their pain has consistently been

TABLE 1
Structural, functional, and neurochemical changes associated with central sensitization

Structural and functional changes in the thalamus, hypothalamus, and amygdala
Hyperexcitability of the cell membrane of central neurons, decreased action potential threshold, increased synaptic strength, decreased descending inhibitory transmission, reduced activation threshold, and enlarged receptive fields
Loss of gray matter volume in the anterior and posterior cingulate cortex and prefrontal cortex
Heightened functional activity within the somatosensory cortex (sensory processing), insula (emotional context of sensation, sensory appraisal), and amygdala (mood processing)
Increased temporal summation (leading to increasing ascending sensory amplification) and reduced conditioned pain modulation (reduction in descending inhibitory signals)
Maladaptive central and peripheral neuroplasticity
Hypothalamic-pituitary-adrenal axis changes
Hyperactive sympathetic nervous system and endogenous opioid system
Changes in neurotransmitter concentrations in the cerebrospinal fluid

Adapted from information in reference 1.

shown to enhance their ability to understand and manage their symptoms.[6–9] We believe that educating patients and families about central sensitization empowers them to better appreciate what is going on in their bodies and helps them identify the best ways to manage their symptoms.

This article aims to enhance clinicians' knowledge about central sensitization and to help them teach patients and families about its role in chronic symptoms—leading, we hope, to more realistic patient expectations and better outcomes.

THE ROLE OF CENTRAL SENSITIZATION IN CHRONIC PAIN AND OTHER SYMPTOMS

The term central sensitization was coined by Woolf and King[10] in 1989 after studies in rats showed that neurons in the spinal cord become hyperexcitable over time after injury. Subsequent studies showed that central sensitization can be maintained with or without continued peripheral input, and that chemical, structural, and functional changes in the central nervous system may ultimately lead to a persistent, heightened state of neural reactivity.[11,12]

In this pathophysiologic state, the central nervous system is hyperexcited even in the absence of sensory stimuli, and sensory messages are amplified, whether internal or external to the body. This amplification often leads to chronic, widespread, and migratory pain, chronic fatigue, sensory hyperresponsiveness, and many other symptoms. The pain usually is in disparate or incongruent bodily regions, and medical evaluations reveal nothing helpful as to the cause.[1,13] The pathophysiologic changes associated with central sensitization are summarized in **Table 1.**[1]

The 'trifecta' of central sensitization

Overall, these changes create the "trifecta" of central sensitization:

- **Hyperalgesia**, in which a painful stimulus becomes associated with even more pain.
- **Allodynia**, in which a previously nonpainful stimulus now causes pain. Many patients with central sensitization say that a hug or a pat on the back hurts them, clothing irritates their skin, or a heavy blanket exerts painful pressure.
- **Global sensory hyperresponsiveness**, in which the patient is extremely affected by external and internal stimuli. For example, patients with central sensitization may be very sensitive to bright lights, loud noises, smells, foods, and medications, as well as to internal stimuli such as their heartbeat or peristalsis in their gastrointestinal tract.[12,14]

By asking patients if and how they experience these phenomena, and providing real-life examples, clinicians will be able to identify core features of central sensitization.

Mechanisms of acute vs chronic pain

But how does this all occur?

The enhanced response is in part due to neuroplasticity, ie, the ability of the central nervous system to adapt over time.

In the past, pain processing was thought of as a nebulous, passive relay between noxious stimuli and the parts of the brain responsible for interpreting pain (nociception). This model posited the existence of specific pain pathways, activated only by peripheral painful stimuli, and suggested that the intensity and duration of pain depended solely on these inputs.[14] Acute pain therefore was an adaptive, protective function that occurred when a potentially harmful stimulus activated a peripheral nerve, which transported that message to the spinal cord, which carried it to the brain. It alerted an organism to threats and helped it escape from danger and recover from injury.[15]

Now we know that the process is more complicated. When a peripheral nerve receives a stimulus, the message is reviewed neurochemically. Some neurochemicals amplify the message, whereas others inhibit it. Notably, the inhibiting and amplifying effects originate in the brain, and the modulating messages are sent back down through dedicated neural pathways.[16] Usually, the system is well balanced, so that if the brain perceives a stimulus as potentially harmful, the organism will respond to protect itself, whereas nonthreatening stimuli are minimized and do not come to the level of conscious awareness.

The spinal-gate control theory, proposed in 1965 by Melzack and Wall,[17] introduced the concept of pain modulation and explained how acute pain differs from chronic pain. In chronic pain, neuroplasticity has primed the nerves to be more sensitive to stimulation, and pain signaling is not just a protective response to noxious stimuli. Rather, pain signals are a consequence of maladaptive changes within the nervous system (neuropathy) and are not necessarily a response to acute nociceptive concerns.

Various neuroplastic factors (including central sensitization, peripheral sensitization, and descending neuromodulation) and risk factors (including genetic variants, medical and psychological comorbidities, medications, and psychosocial factors) may explain why acute pain becomes chronic in some people.[18] Although chronic pain previously was believed to arise from nociception or neuropathy, a third category of pain, termed *nociplastic pain*, has been proposed to describe the increased sensitivity caused by the altered function of sensory pathways.[19] With central sensitization, the central nervous system can "change, distort or amplify pain, increasing its degree, duration, and spatial extent in a manner that no longer directly reflects the specific qualities of peripheral noxious stimuli, but rather the particular functional states of circuits in the [central nervous system]."[13]

Thus, patients with central sensitization may perceive pain from normally nonpainful stimuli (allodynia) and experience greater pain from painful stimuli (hyperalgesia). Affected neurons can have spontaneous autonomous activity, lower thresholds for activation or pain, and wider receptive fields (the pain becomes more diffuse and less definable).[20]

A patient with central sensitization genuinely feels sensations differently and more intensely than someone without central sensitization. For example, a patient experiencing chronic pain in a well-defined site may observe with time that the pain becomes more diffuse, less defined, and associated with other seemingly unrelated symptoms such as fatigue, headaches, unrefreshing sleep, mood changes, and gastrointestinal concerns. The patient may also relate heightened sensitivities and, as a result, may fear that something new or sinister is happening.

Central sensitization syndrome

What is the role of central sensitization in non–pain-related symptoms? The consensus is that changes that lead to pain origination and amplification similarly lead to many other symptoms.[1] Although pain is a primary focus when discussing central sensitization, this condition is complex, with multiple nonpainful symptoms.

The unifying term *central sensitization syndrome* was proposed by Yunus[21] to include overlapping symptoms such as pain, fatigue, sleep disorders, paresthesias, cognitive difficulties, and overlapping conditions such as irritable bowel syndrome, restless leg syndrome, interstitial cystitis, temporomandibular joint disorder, and others. The concept of various coexisting conditions and symptoms all being based on central sensitization has been recognized by the National Institutes of Health with the term *chronic overlapping pain conditions*.[22]

These conditions have gained greater attention recently, particularly because they share many features with post-COVID-19 syndrome, including chronic pain and fatigue, postural orthostasis, mood and sleep disturbances, and gastrointestinal symptoms.[23] Although additional research is needed to identify the underlying pathophysiologic changes in post-COVID-19 syndrome, we believe that many of the underlying features of central sensitization will be directly applicable.

Other factors that affect an individual's experience of central sensitization are being explored. These can be protective or pathologic, depending on the circumstances, and they include the autonomic nervous system, endocrine and immune systems, and mechanisms by which the brain responds to neural stimuli. For example, glial cells and neuroinflammation are now known to be key components of the pain experience and are targets of ongoing research.[24] Studies have investigated the impact of sleep dysregulation on the development of central sensitization (by means of glial cell activation and neuroinflammatory changes) and the need for sleep hygiene as part of central sensitization-focused therapy.[25,26]

EDUCATING PATIENTS ABOUT PAIN PHYSIOLOGY

Educating patients about pain physiology and providing them with management strategies helps them reduce the intensity of their symptoms.

Although the field of pain research has seen tremendous advances in recent years, many symptoms and conditions still evade concrete diagnoses and lack effective treatments. As a result, many patients are dissatisfied with their medical care, and they often continue to search for a cure.

Nijs et al[8] described how patients who are confused about their pain and believe that they have not received an appropriate diagnosis often assume that their pain indicates that something terrible is happening in their body. Fear of the unknown and excessive efforts to identify the cause can lead patients to have maladaptive perceptions of their symptoms. With this mindset, patients are less able to manage their symptoms, leading to poorer function and an overall lower quality of life. Therefore, successful management of symptoms crucially begins with changing the thought process by educating patients about basic neuroanatomy, physiology, and the role of central sensitization in the nociplastic pain experience.

Sharing information about central sensitization in a way that can be readily understood will increase hope and motivation for those experiencing chronic pain and other long-term symptoms.[8] A randomized controlled trial showed that patients who received education about pain physiology worried less about their symptoms and reported better physical function, better mood, more energy, less pain, and overall improved general health perceptions than patients who received generic self-management education.[9] Another study showed that neuroscience education in addition to standard nonpharmacologic treatments was associated with reduced pain severity and disability and improved mental and physical function.[27]

Tailoring learning methods helps build trust

By teaching patients and their families about central sensitization and the differences between acute peripheral pain and centralized nociplastic pain, clinicians can establish trust and empower patients by helping them understand what is happening in their bodies. And trust and empowerment help patients change how they approach and experience pain.

No single educational method is suitable for all patients. Principles of adult learning should be considered, and participants should be offered various options. Face-to-face education combined with written materials offers an ideal learning experience with more sustained outcomes than written materials alone.[8,9,28] In our practice we use didactic lectures, handouts and other materials, hands-on demonstrations, visual aids, videos, Internet resources, discussions, and storytelling. Topics include patient experience, diagnostic criteria, physiology of the central nervous system and autonomic nervous system, the cycle of pain, symptom-focused behavior, stress management, diaphragmatic breathing, and biofeedback.

The technical nature of this content can be overwhelming for the layperson, so after assessing the individual's readiness to learn, the information should be conveyed in an understandable manner, using plain language. Additionally, researchers are constantly publishing new findings about central sensitization, which clinicians should be aware of and discuss with patients.

Education could occur across the continuum of care, outpatient and inpatient. Continuing patient education is appropriate even in long-term care settings because many residents are living longer with chronic pain and multiple comorbid conditions.

EVIDENCE-BASED NONPHARMACOLOGIC TREATMENT

Evidence-based strategies exist for improving physical function and quality of life. Although the functional status of patients with central sensitization may vary widely, self-management strategies such as stress management, diaphragmatic breathing, relaxation, mindfulness, graded exercise, and cognitive behavior therapy can be implemented. Depending on the patient's level of impairment, the intervention may be focused and brief, or it may need to be in-depth, interdisciplinary, and rehabilitative.[29]

A helpful way to begin is by guiding patients

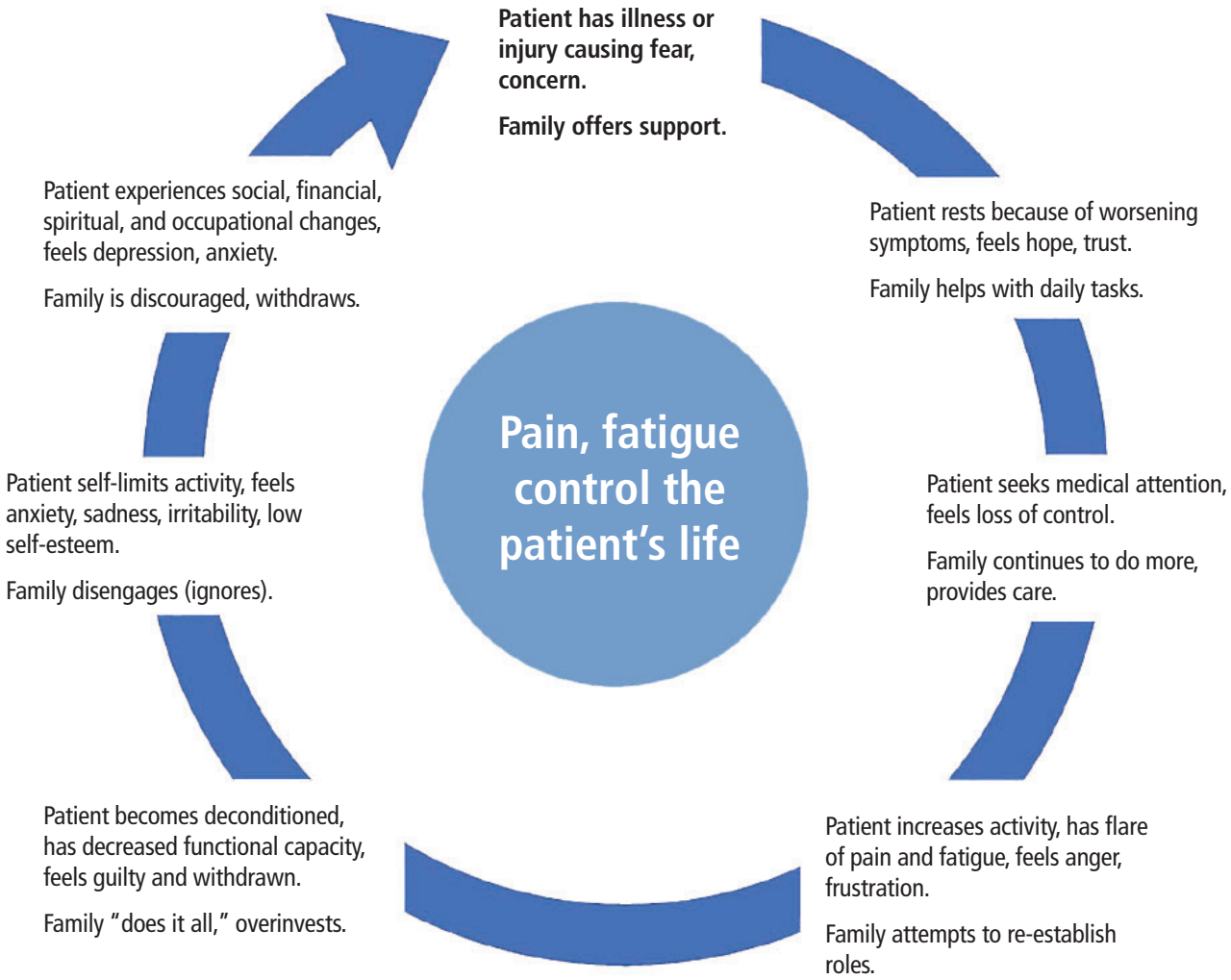


Figure 1. The cycle of pain and fatigue in central sensitization, showing patient behaviors and emotions and family response.

through an activity that makes them think about how they got to where they currently are in their pain journey. This activity helps identify triggers that may perpetuate the pain cycle and contribute to other harmful actions, such as symptom-focused behaviors, symptom hypervigilance, activity avoidance, and decreased socialization.

Although each person's history is different, patients report similar behaviors, emotions, and family responses regarding their chronic symptoms. **Figure 1** shows how a patient can get caught in a downward spiral. Such patients often consider pain to be excessively threatening, have lower pain tolerance, and have hypervigilance with catastrophic thoughts. Family members go through their own cycle.

Clinicians should seize the opportunity to give hope by educating and empowering patients to take an active rather than passive role in their recovery. Helping patients break free from the cycle of pain and symptom-focused behavior requires them to shift their perspective from an external to an internal locus of control. This change requires education and

TABLE 2
Central sensitization: Turning negatives into positives

Negative or distorted beliefs	Positive and rational beliefs
Because of my pain or symptoms, I am no longer the person I was. I no longer feel loved and appreciated.	I may have changed somewhat physically, but I am more than just a physical being. I am worthy of love and of being appreciated for all that I am.
People reject me because they can see I am disabled.	I am not disabled. I have goals and dreams and can accomplish many things.
I used to be able to do so many things—now I can't do anything. I am no longer competent or adequate.	I can do a lot more than I thought. Almost everything I used to do, I can still do to some degree.
I can't do anything because of my symptoms.	With moderation, I can be actively involved in life. I just need to pace myself and take breaks.
I have no control over my happiness. The pain or symptoms control me.	I can control my happiness. I can be happy and enjoy life even when I have pain or other symptoms.
People think I'm faking this.	People sometimes need help understanding medical issues. I can share what I know about chronic pain.
If my symptoms act up when I'm out with friends, I'll be embarrassed and ruin things for everyone.	I can help my friends understand. I can take breaks and still enjoy myself when I'm with them.
Medical science can do so much. Surely there must be a cure for my symptoms.	Even if medical science can't fix everything, I can choose my response and focus on self-care skills.
People at work are upset with me. I have restrictions and they think I am not doing my share.	I will do the best job I can. If people don't understand, that's their problem—I can't please everyone.

From Mayo Clinic Patient Education. Managing your Fibromyalgia (MC2593-100). Rochester, MN: Mayo Clinic, 2017, pp. 7 & 32; used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.

consistency on the part of the patient. Acceptance of pain and a willingness to engage in self-management have been shown to improve functional outcomes.[30,31]

To help patients gradually work self-management skills and strategies into their daily lives, it is essential to set goals. For each new strategy, clinicians can help patients write down specific, realistic, and measurable goals. Patients should then write down the specific steps needed to achieve the goals, as they are then more likely to do the work and follow through. Motivational communication skills such as engaging, focusing, and planning can help patients begin the next step of their journey.[32]

Cognitive behavior therapy and related techniques

Cognitive behavior therapy involves identifying harmful thoughts, emotions, and behaviors and restructuring them into more beneficial ones (**Table 2**). Patients should know that they can replace maladaptive strategies with more appropriate ones that will help lessen their symptoms.

This cognitive restructuring or reframing is done with a trained clinician for a limited time. This approach has been highly successful in helping patients with chronic symptoms improve their overall quality of life and reduce their symptom burden.[33–37]

Various forms of cognitive behavior therapy are available for specific symptoms such as anxiety, depression, pain, or insomnia. *Acceptance and commitment therapy* was developed in the mid-1990s as an action-oriented approach that focuses less on controlling or changing negative thoughts and behaviors and concentrates more on helping an individual accept a negative obstacle such as pain or central sensitization and to move past it, despite what they are experiencing.[34,36,38] Acceptance in this context is not about resigning oneself to chronic pain. Rather, it is about adapting and learning to respond to symptoms in a healthier manner. Another treatment that can be considered is *emotional awareness and expression therapy*.[39]

These approaches can help the patient shift the focus away from symptoms and help build new memory pathways through neuroplasticity.

TABLE 3
Examples of graded exercise recommendations for self-management

Activity	Examples	Progression	Frequency
Flexibility	Head-to-toe stretches	Initially, may need to break up throughout the day (if too much to do in 1 session)	Once daily
Aerobic exercise	Walking, biking, swimming	Initial duration depends on the patient's comfort level (eg, may be 5 minutes) Gradually increase time by 2–5 minutes every 2 weeks	30 minutes, 3 times a week[a]
Strength training	Hand weights, resistance bands, water bottles	Start slowly Gradually increase resistance or weight	2 times a week[a]

[a]Alternate aerobic exercise days and strength training days. For example, aerobic exercise could occur on Mondays, Wednesdays, and Fridays. Strength training could occur on Tuesdays and Thursdays.

From reference 44: Abril A, Bruce BK. Mayo Clinic Guide to Fibromyalgia: Strategies to Take Back Your Life. Rochester, MN: Mayo Foundation for Medical Education and Researech, 2019; used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.

Stress management

Stress management has a key role in helping patients manage their anxiety and reduce catastrophizing, and it also directly affects physical symptoms by dampening the autonomic stress response.[37] Stress-management techniques such as diaphragmatic breathing, relaxation, biofeedback, and mindfulness-based stress reduction can help decrease sympathetic (fight-or-flight) activity.

Mindfulness-based stress reduction promotes neuroplasticity and reduces sympathetic drive. Mindfulness is a skill in which people focus on the present moment, including emotions and physical state, and use meditation, yoga, and focused breathing to lessen symptoms related to central sensitization.[40]

According to Keefer and Mandal,[34] this approach promotes downregulation of pain pathways and also helps improve the emotional experience of pain. Adler-Neal and Zeidan[40] reported that cognitive behavior therapy and mindfulness-based stress reduction helped decrease functional connectivity in areas of the brain associated with anticipation, emotional evaluation, and sensory discrimination, resulting in less pain and catastrophizing. Chiesa and Serretti[41] showed that the practice of mindfulness reduced pain-related depressive symptoms and stress levels while improving quality of life and increasing pain acceptance.

Graded exercise

Studies have examined the benefits of exercise (flexibility, aerobic, and strengthening) for patients with chronic pain. Ambrose and Golightly[42] concluded that exercise not only decreased pain but improved overall physical function, sleep quality, and cognitive function.

Unfortunately, after being told to exercise, many patients get into a cycle of overdoing it on a "better" day, only to have more severe symptoms later. This exercise-induced exacerbation can cause patients to associate pain with exercise, termed a *pain memory*.[43]

Graded exercise helps create new memory pathways in the brain, which will decrease the perception of pain and fear of movement

To prevent this cycle, exercise should be graded: the patient should exercise at a low, tolerable level and then gradually increase the duration and intensity. Nijs et al[43] recommend an approach based on goals such as duration, number of repetitions, and distance rather than on pain levels. **Table 3** shows an example plan with graded exercise recommendations.[44]

Initially, some patients with central sensitization find that even small amounts of exercise, movement, or activity provoke symptoms, and this can be extremely frustrating and discouraging. The important point to communicate to patients is that graded exercise, movement, and activity strengthen the body in a sustainable manner over time. Graded exercise helps create new memory pathways in the brain,

which will decrease the perception of pain and fear of movement.[43]

Tips on implementing a treatment strategy

To lessen symptoms and enhance quality of life, patients must be ready to transition from a diagnostic mindset to a rehabilitative one. Thus, before starting any treatment, they should understand their symptoms, previous diagnostic results, the need to avoid unnecessary or repetitive diagnostic evaluations (especially those with low value or diagnostic utility), the process of central sensitization, and the importance of using strategies that target both the central (nociplastic) and peripheral mechanisms of symptoms.[1,13,29,45]

Pharmacologic treatments can include nonsteroidal anti-inflammatory drugs and topical agents aimed at specific peripheral pain generators, if present, as well as neuromodulators (eg, pregabalin, gabapentin, amitriptyline, nortriptyline, duloxetine, milnacipran) that aim to mitigate several of the neurochemical and functional pathophysiologic changes present in central sensitization.[1,13,29] Many patients with central sensitization also have focal sources of pain: for example, a patient with fibromyalgia could also have knee osteoarthritis. Thus, treatment needs to strike a balance between therapies aimed at the central sensitization symptoms and the focal symptoms.

Nonpharmacologic strategies, as described above, are strongly recommended as part of a multimodal rehabilitative approach.[1,13,29] By providing ongoing education about pain physiology (through clinical visits, handouts, articles, videos, trusted online resources) and describing the process of central sensitization as the anchoring framework, clinicians will be far better able to achieve patient acceptance and motivation. Additional nonpharmacologic treatments that are helpful in central sensitization include time management, moderation, physical and occupational therapy, massage therapy, acupuncture, graded exercise therapy, and sleep hygiene.[29]

Our preferred approach is to offer individualized strategies to patients and allow them to determine what will work for them. After the strategies are identified and agreed upon, it is vital to refer patients to the appropriate specialists and to encourage patients to implement these strategies to create new neural pathways. Furthermore, if patients struggle to implement these strategies, they can be encouraged to seek further clinical assistance or an interdisciplinary pain rehabilitation program.

No one-size-fits-all treatment strategy exists for patients with central sensitization. Rather, the lack of a "perfect" strategy highlights the need for bidirectional communication, ongoing patient education, and routine clinical visits.

Clinical visits should initially focus on reviewing the history and diagnostic evaluations, making the appropriate diagnosis, and then transitioning to education about pain physiology and central sensitization. Subsequent visits should focus on implementing a multimodal (pharmacologic and nonpharmacologic) approach, with ongoing visits to ensure treatment compliance and functional improvement.

Clinicians should also attempt to consolidate the care for patients with central sensitization-based conditions or other difficult-to-diagnose ("medically unexplained") conditions rather than provide frequent referrals to subspecialists for additional investigation, as frequent referrals have limited utility and may lead to greater patient dissatisfaction, higher healthcare costs, and, potentially, patient harm.[46]

ACHIEVING THOROUGH AND EMPATHIC CARE OF PATIENTS WITH NOCIPLASTIC PAIN

The educational framework of central sensitization, which validates and explains the patient's experience of pain and other symptoms, is a key factor in the thorough and empathic care of patients with nociplastic pain. Education about their condition is a vital step in the patient's acceptance of and commitment to evidence-based tools to manage their symptoms. The literature supports teaching patients about the basics of central sensitization and nociplastic pain in conjunction with coaching them to implement nonpharmacologic management strategies that help decrease symptoms and improve overall quality of life. Teaching this content is within the scope of clinical practice and is an essential component of high-quality care.

Acknowledgment: *June Oshiro, PhD, ELS, Mayo Clinic, substantively edited the manuscript. The Scientific Publications staff at Mayo Clinic provided proofreading, administrative, and clerical support.*

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Harte SE, Harris RE, Clauw DJ.** The neurobiology of central sensitization. J Appl Behav Res 2018; 23:e12137. https://doi.org/10.1111/jabr.12137
2. **Dahlhamer J, Lucas J, Zelaya C, et al.** Prevalence of chronic pain and high-impact chronic pain among adults—United States, 2016. MMWR Morb Mortal Wkly Rep 2018; 67(36):1001–1006. doi:10.15585/mmwr.mm6736a2
3. **Centers for Disease Control and Prevention.** Understanding the opioid overdose epidemic. Updated June 1, 2022. https://www.cdc.gov/opioids/basics/epidemic.html. Accessed January 25, 2023.
4. **US Centers for Disease Control and Prevention.** National Center for Health Statistics. Provisional drug overdose death counts. Updated January 11, 2023. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm. Accessed March 13, 2023.
5. **Sud A, Buchman DZ, Furlan AD, Selby P, Spithoff SM, Upshur REG.** Chronic pain and opioid prescribing: three ways for navigating complexity at the clinical–population health interface. Am J Public Health 2022; 112(S1):S56–S65. doi:10.2105/AJPH.2021.306500
6. **Louw A, Zimney K, Puentedura EJ, Diener I.** The efficacy of pain neuroscience education on musculoskeletal pain: a systematic review of the literature. Physiother Theory Pract 2016; 32(5):332–355. doi:10.1080/09593985.2016.1194646
7. **Moseley GL, Nicholas MK, Hodges PW.** A randomized controlled trial of intensive neurophysiology education in chronic low back pain. Clin J Pain 2004; 20(5):324–330. doi:10.1097/00002508-200409000-00007
8. **Nijs J, Paul van Wilgen C, Van Oosterwijck J, van Ittersum M, Meeus M.** How to explain central sensitization to patients with 'unexplained' chronic musculoskeletal pain: practice guidelines. Man Ther 2011; 16(5):413–418. doi:10.1016/j.math.2011.04.005
9. **Van Oosterwijck J, Meeus M, Paul L, et al.** Pain physiology education improves health status and endogenous pain inhibition in fibromyalgia: a double-blind randomized controlled trial. Clin J Pain 2013; 29(10):873–882. doi:10.1097/AJP.0b013e31827c7a7d
10. **Woolf CJ, King AE.** Subthreshold components of the cutaneous mechanoreceptive fields of dorsal horn neurons in the rat lumbar spinal cord. J Neurophysiol 1989; 62(4):907–916. doi:10.1152/jn.1989.62.4.907
11. **Nijs J, Van Houdenhove B.** From acute musculoskeletal pain to chronic widespread pain and fibromyalgia: application of pain neurophysiology in manual therapy practice. Man Ther 2009; 14(1): 3–12. doi:10.1016/j.math.2008.03.001
12. **Yunus MB.** Editorial review: an update on central sensitivity syndromes and the issues of nosology and psychobiology. Curr Rheumatol Rev 2015; 11(2):70–85. doi:10.2174/1573397111102150702112236
13. **Woolf CJ.** Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011; 152(3 suppl):S2–S15. doi:10.1016/j.pain.2010.09.030
14. **Latremoliere A, Woolf CJ.** Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009; 10(9):895–926. doi:10.1016/j.jpain.2009.06.012
15. **Wood PB.** Variations in brain gray matter associated with chronic pain. Curr Rheumatol Rep 2010; 12(6):462–469. doi:10.1007/s11926-010-0129-7
16. **Butler DS, Moseley GL.** Explain Pain. 2nd ed. Adelaide, Australia: NOI Group Publications; 2013.
17. **Melzack R, Wall PD.** Pain mechanisms: a new theory. Science 1965; 150(3699):971–979. doi:10.1126/science.150.3699.971
18. **McGreevy K, Bottros MM, Raja SN.** Preventing chronic pain following acute pain: risk factors, preventive strategies, and their efficacy. Eur J Pain Suppl 2011; 5(2):365–372. doi:10.1016/j.eujps.2011.08.013
19. **Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W.** Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet 2021; 397(10289):2098–2110. doi:10.1016/S0140-6736(21)00392-5
20. **Fleming KC, Volcheck MM.** Central sensitization syndrome and the initial evaluation of a patient with fibromyalgia: a review. Rambam Maimonides Med J 2015; 6(2):e0020. doi:10.5041/RMMJ.10204
21. **Yunus MB.** Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. Best Pract Res Clin Rheumatol 2007; 21(3):481–497. doi:10.1016/j.berh.2007.03.006
22. **Maixner W, Fillingim RB, Williams DA, Smith SB, Slade GD.** Overlapping chronic pain conditions: implications for diagnosis and classification. J Pain 2016; 17(9 suppl):T93–T107. doi:10.1016/j.jpain.2016.06.002
23. **Bierle DM, Aakre CA, Grach SL, et al.** Central sensitization phenotypes in post acute sequelae of SARS-CoV-2 infection (PASC): defining the post COVID syndrome. J Prim Care Community Health 2021; 12:21501327211030826. doi:10.1177/21501327211030826
24. **Milligan ED, Watkins LR.** Pathological and protective roles of glia in chronic pain. Nat Rev Neurosci 2009; 10(1):23–36. doi:10.1038/nrn2533
25. **de Tommaso M, Delussi M, Vecchio E, Sciruicchio V, Invitto S, Livrea P.** Sleep features and central sensitization symptoms in primary headache patients. J Headache Pain 2014; 15(1):64. doi:10.1186/1129-2377-15-64
26. **Nijs J, Loggia ML, Polli A, et al.** Sleep disturbances and severe stress as glial activators: key targets for treating central sensitization in chronic pain patients? Expert Opin Ther Targets 2017; 21(8):817–826. doi:10.1080/14728222.2017.1353603
27. **Malfliet A, Kregel J, Meeus M, et al.** Patients with chronic spinal pain benefit from pain neuroscience education regardless the self-reported signs of central sensitization: secondary analysis of a randomized controlled multicenter trial. PM R 2018; 10(12):1330–1343.e1. doi:10.1016/j.pmrj.2018.04.010
28. **Sluka KA.** Mechanisms and Management of Pain for the Physical Therapist. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2016.
29. **Macfarlane GJ, Kronisch C, Dean LE, et al.** EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 2017; 76(2):318–328. doi:10.1136/annrheumdis-2016-209724
30. **Åkerblom S, Perrin S, Rivano Fischer M, McCracken LM.** The mediating role of acceptance in multidisciplinary cognitive-behavioral therapy for chronic pain [published correction appears in J Pain 2016; 17(10):1135–1136]. J Pain 2015; 16(7):606–615. doi:10.1016/j.jpain.2015.03.007
31. **Amris K, Luta G, Christensen R, Danneskiold-Samsøe B, Bliddal H, Wæhrens EE.** Predictors of improvement in observed functional ability in patients with fibromyalgia as an outcome of rehabilitation. J Rehabil Med 2016; 48(1):65–71. doi:10.2340/16501977-2036
32. **Morton K, Beauchamp M, Prothero A, et al.** The effectiveness of motivational interviewing for health behaviour change in primary care settings: a systematic review. Health Psychol Rev 2015; 9(2):205–223. doi:10.1080/17437199.2014.882006
33. **Eller-Smith OC, Nicol AL, Christianson JA.** Potential mechanisms underlying centralized pain and emerging therapeutic interventions. Front Cell Neurosci 2018; 12:35. doi:10.3389/fncel.2018.00035
34. **Keefer L, Mandal S.** The potential role of behavioral therapies in the management of centrally mediated abdominal pain. Neurogastroenterol Motil 2015; 27(3):313–323. doi:10.1111/nmo.12474
35. **Nash VR, Ponto J, Townsend C, Nelson P, Bretz MN.** Cognitive behavioral therapy, self-efficacy, and depression in persons with chronic pain. Pain Manag Nurs 2013; 14(4):e236–e243. doi:10.1016/j.pmn.2012.02.006
36. **Thorsell J, Finnes A, Dahl J, et al.** A comparative study of 2 manual-based self-help interventions, acceptance and commitment therapy and applied relaxation, for persons with chronic pain [published correction appears in Clin J Pain 2013; 29(5):469]. Clin J Pain 2011; 27(8):716–723. doi:10.1097/AJP.0b013e318219a933
37. **Varvogli L, Darviri C.** Stress management techniques: evidence-based procedures that reduce stress and promote health. Health Sci J 2011; 5(2):74–89.
38. **Vowles KE, Thompson M.** Acceptance and commitment therapy for

chronic pain. In: McCracken LM, ed. Mindfulness and Acceptance in Behavioral Medicine: Current Theory and Practice. Oakland, CA: New Harbinger Publications, Inc; 2011: 31–60.
39. **Lumley MA, Schubiner H, Lockhart NA, et al.** Emotional awareness and expression therapy, cognitive behavioral therapy, and education for fibromyalgia: a cluster-randomized controlled trial. Pain 2017; 158(12):2354–2363. doi:10.1097/j.pain.0000000000001036
40. **Adler-Neal AL, Zeidan F.** Mindfulness meditation for fibromyalgia: mechanistic and clinical considerations. Curr Rheumatol Rep 2017; 19(9):59. doi:10.1007/s11926-017-0686-0
41. **Chiesa A, Serretti A.** Mindfulness-based interventions for chronic pain: a systematic review of the evidence. J Altern Complement Med 2011; 17(1):83–93. doi:10.1089/acm.2009.0546
42. **Ambrose KR, Golightly YM.** Physical exercise as non-pharmacological treatment of chronic pain: why and when. Best Pract Res Clin Rheumatol 2015; 29(1):120–130. doi:10.1016/j.berh.2015.04.022
43. **Nijs J, Lluch Girbés E, Lundberg M, Malfliet A, Sterling M.** Exercise therapy for chronic musculoskeletal pain: innovation by altering pain memories. Man Ther 2015; 20(1):216–220. doi:10.1016/j.math.2014.07.004
44. **Abril A, Bruce BK.** Mayo Clinic Guide to Fibromyalgia: Strategies to Take Back Your Life. Rochester, MN: Mayo Foundation for Medical Education and Research, 2019.
45. **Abeles AM, Abeles M.** The clinical utility of a positive antinuclear antibody test result. Am J Med 2013; 126(4):342–348. doi:10.1016/j.amjmed.2012.09.014
46. **Husain M, Chalder T.** Medically unexplained symptoms: assessment and management. Clin Med (Lond) 2021; 21(1):13–18. doi:10.7861/clinmed.2020-0947

Address: *Mary M. Volcheck, MSN, RN, Department of Nursing, Mayo Clinic, 200 First Street SW, Rochester, MN 55905; volcheck.mary@mayo.edu*

Cleveland Clinic
Center for Continuing Education

JOIN THE CME COMMUNITY

Want to make sure you are updated on medical education that is available to you?

Need to earn continuing education credits?

Join our CME Community!

By becoming a part of the Cleveland Clinic Center for Continuing Education CME Community, you will always be on the cutting edge of educational opportunities available.

SIGN UP TODAY! **CCFCME.ORG/CMECOMMUNITY**

How to earn *AMA PRA Category 1 Credit*™ and ABIM MOC points

AMA/PRA Category 1 Credit™

To read articles as CME activities and claim credit, go to www.ccjm.org, click on the "CME/MOC" menu, and then "Articles." Find the articles that you want to read as CME activities and click on the appropriate links. After reading an article, click on the link to complete the activity. You will be asked to log in to your MyCME account (or to create an account). Upon logging in, select "CME," complete the activity evaluation, and print your certificate.

Call 216-444-2661 or e-mail ccjm@ccf.org with questions.

Maintenance of Certification (MOC) Points

All *Cleveland Clinic Journal of Medicine* CME activities are eligible for ABIM MOC points. Physicians may claim MOC points in addition to CME credit.

Follow the instructions for completing and claiming credit for CME activities.

When you log into your MyCME account, select "CME & MOC" and enter your ABIM identification number and your date of birth. The system will store this information after you enter it the first time.

Complete the quiz and evaluation and print your CME certificate.

April 2023 CME/MOC activity

Estimated time to complete the activity: up to 1 hour

How does climate change impact our patients?

Release date: April 1, 2023
Expiration date: March 31, 2024

FINANCIAL DISCLOSURES: In accordance with the Standards for Integrity and Independence issued by the Accreditation Council for Continuing Medical Education (ACCME), The Cleveland Clinic Center for Continuing Education mitigates all relevant conflicts of interest to ensure CE activities are free of commercial bias.

AUTHOR AND STAFF DISCLOSURES: Authors' potential conflicts of interest are disclosed within their articles. *Cleveland Clinic Journal of Medicine's* staff disclose the following financial relationships that may be relevant to their editorial roles: Dr. Brian F. Mandell (Editor in Chief) reports teaching and speaking for Genentech; and consulting for Horizon Pharma. Dr. Kristin Highland (Associate Editor) has disclosed financial interests (consulting, research, teaching, and speaking) with Actelion Pharmaceuticals, Bayer Healthcare, Boehringer Ingelheim, Eiger Biopharmaceuticals, Gententech, Gossamer Bio, Lilly, Reata Pharmaceuticals, United Therapeutics, and Viela Bio. Dr. Christian Nasr (Associate Editor) reports service on advisory committees or review panels for Exelixis, Horizon Pharma, Neurogastrx, and Nevro Corp.; and consulting for Siemens.

DISCLAIMER: The information in these educational activities is provided for general medical education purposes only and is not meant to substitute for the independent medical judgment of a physician relative to diagnostic and treatment options of a specific patient's medical condition. The viewpoints expressed in these CME activities are those of the authors. They do not represent an endorsement by The Cleveland Clinic Foundation. In no event will The Cleveland Clinic Foundation be liable for any decision made or action taken in reliance upon the information provided through these CME activities.

CME ACCREDITATION:
In support of improving patient care, Cleveland Clinic Center for Continuing Education is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The Cleveland Clinic Center for Continuing Education designates this journal-based CME activity for a maximum of *1.0 AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Participants claiming CME credit from this activity may submit the credit hours to the American Osteopathic Association for Category 2 credit.

AMERICAN BOARD OF INTERNAL MEDICINE (ABIM):
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Please Note: To receive MOC you must select the MOC option during the online credit claiming process and complete the required steps. ABIM MOC points will be reported within 30 days of claiming credit.