

# Clinical Neurology Update

from NEJM Group

■ Roundtable:  
Advances in  
Parkinson's  
Disease

■ Topic Update:  
Treatment of  
Multiple Sclerosis

■ Treatment  
of Acute  
Ischemic Stroke

■ Long-Term  
Neurological  
Effects of  
Covid-19

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(800) 843-6356, or email [nejmcust@mms.org](mailto:nejmcust@mms.org).

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## FROM the Editor

The pace of development in treatment of neurological disease has rapidly evolved recently. The days of the neurologist arriving at a difficult diagnosis, often without a palatable treatment option, are disappearing. A new day has arrived in neuromedicine, and in this issue, we will review a selection of the most exciting and emerging updates in clinical neurology. We kick off the issue with a roundtable discussion of the most rapidly growing neurological disease, Parkinson's. Bastiaan Bloem from Radboud University, Ray Dorsey from the University of Rochester, Tanya Simuni from Northwestern University, and I together tackle Parkinson's-related advances and discuss the exciting developments in the pipeline.

Pooja Khatri, from the University of Cincinnati, updates us on the treatment of acute ischemic stroke. Teshamae Monteith, from the University of Miami, brings us up to speed on CGRP, toxin therapy, neuromodulation, and other exciting approaches for migraine. Tom Solomon, Benedict Michael, and Tim Nicholson, all from the U.K., teach us about the long-term neurological and neuropsychiatric effects of Covid-19. Bianca Weinstock-Guttman and Dejan Jakimovski, from the University at Buffalo, address exciting advances in the treatment of multiple sclerosis. Page Pennell from Harvard Medical School updates us on the evolution in our understanding of the underpinnings of seizures and progress in the pipeline for medical and surgical interventions. Finally, Michael Jaffee, from the University of Florida, and Breton Asken, from the University of California, San Francisco, update us on the treatment of concussion.

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We are excited to bring you all of these updates in clinical neurology in a single issue.

### Michael S. Okun, MD, Editor

Michael S. Okun obtained his M.D. with honors from the University of Florida as part of the cooperative PIMS program. He was the chief resident in neurology at the University of Florida. He was fellowship trained by Mahlon DeLong, Jerrold Vitek, and Ray Watts at Emory University in Atlanta before founding the movement disorders program at the University of Florida.

He is currently Chair of Neurology, Professor and Executive Director of the Norman Fixel Institute for Neurological Diseases at the University of Florida Health College of Medicine. The institute he cofounded with Dr. Kelly D. Foote uniquely comprises 123 interdisciplinary faculty members from 35 departments, all dedicated to care, outreach, education, and research. Dr. Okun was instrumental in the construction of a one-stop patient-centered clinical research experience for national and international patients seeking care at the University of Florida. This novel care and research delivery model has since been named the service and science hub model of care. The university-based center draws national and international visitors interested in deploying this innovative clinical-research model.

Dr. Okun has served as the National Medical Advisor for the Parkinson's Foundation since 2006 and as the Medical Advisor for Tyler's Hope for a Dystonia Cure since its inception. He has been supported by grants from the National Institutes of Health, the Smallwood Foundation, the Tourette Association of America, the Parkinson Alliance, the Bachmann-Strauss Foundation, the Parkinson's Foundation, and the Michael J. Fox Foundation. Dr. Okun has an active research career exploring nonmotor basal ganglia brain features and currently holds two NIH R01 grants and several foundation grants exploring various aspects of deep brain stimulation and neuromodulation. Dr. Okun has been an integral part of some of the pioneering studies exploring the cognitive, behavioral, and mood effects of brain stimulation, and since 2005, his laboratory has been working to uncover the electrical brain signals associated with human tic. He has also partnered with doctors Ayse Gunduz and Kelly Foote to develop a first generation of closed-loop, adaptive, deep-brain stimulation approaches. Dr. Okun was the founding principal investigator for the International Database and Public Registry for Tourette Deep Brain Stimulation. He and his group have contributed data to support the FDA approval of several device-related approaches now used to treat human disease.

Dr. Okun holds the Adelaide Lackner Professorship in Neurology and has published 406 peer-reviewed articles, 80 review articles, and 10 books, including the poetry collection *Lessons from the Bedside* and his most recent book *Ending Parkinson's Disease*. His book *Parkinson's Treatment: 10 Secrets to a Happier Life* has been translated into more than 20 languages. Dr. Okun was recognized in a 2015 White House ceremony by the Obama administration as a Champion of Change for Parkinson's Disease.

## Roundtable

# Advances in Parkinson's Disease

**Michael S. Okun, MD**, Executive Director, Fixel Institute for Neurological Diseases, University of Florida McKnight Brain Institute, Gainesville, and *NEJM Journal Watch Neurology* editorial board member, recently led a roundtable discussion on the latest research in the treatment of Parkinson's disease with **Bastiaan R. Bloem, MD, PhD, FRCPE**, Director, Radboudumc Center of Expertise for Parkinson & Movement Disorders, Department of Neurology, Radboud University Medical Center, Nijmegen, the Netherlands; **Ray Dorsey, MD**, David M. Levy Professor of Neurology and Director of the Center for Health + Technology, University of Rochester Medical Center, Rochester, NY; and **Tanya Simuni, MD, FAAN**, Arthur C. Nielsen Professor of Neurology Division Head, Parkinson's Disease and Movement Disorders Center, Northwestern University Feinberg School of Medicine. Here is a summary of their conversation.

Parkinson's disease is now the world's fastest-growing neurological disorder (*J Parkinsons Dis* 2018; 8:S3). Over the past 25 years, the number of individuals with Parkinson's worldwide has more than doubled, to 6.3 million, and absent a change in trajectory will double again in the coming generation. In the U.S., prevalence has increased 35% in the last decade alone (Dorsey R et al. *Ending Parkinson's Disease: A Prescription for Action*. PublicAffairs; 2020). If this expansion continues unchecked, it will be medically and economically devastating. To discuss the latest information and advances in treating Parkinson's disease, we convened an expert panel of neurologists.

**MO: We know that aging of the population is not solely driving the rise in Parkinson's disease cases. What else is contributing?**

**BB:** Yes, aging obviously plays a role because the risk of developing Parkinson's disease increases with age, but there is clearly more at work than aging alone. Improved diagnostic tests are not a good explanation; the diagnosis is still very much based on history-taking and a good

neurological examination, just as we did 50 or 100 years ago. If we look at rates globally, the areas of the world that have undergone the most rapid industrialization have the highest rates of increase in Parkinson's disease.

**TS:** The prevalence of Parkinson's disease, even adjusted for age, has increased over 20% (*Lancet Neurol* 2018; 17:939). Environmental factors such as air pollution, certain pesticides, and industrial chemicals like trichloroethylene are probably playing a crucial role. This important role of environmental pollution may partially explain why Parkinson's disease was distinctly rare prior to its first description by James Parkinson in the year 1817. James Parkinson, interestingly, wrote his essay in London at a time when the Industrial Revolution was responsible for a great deal of pollution.

**MO: What is the economic impact of Parkinson's disease?**

**RD:** The Michael J. Fox Foundation recently conducted an analysis estimating the economic cost of Parkinson's in the U.S. to be over \$50 billion, which translates to \$50,000 per person diagnosed with the disease (*NPJ Parkinsons Dis* 2020; 6:15).

**TS:** Half of the cost for Parkinson's disease is attributable to direct health care expenditures and the other half to lost labor productivity and supportive care.

**BB:** The biggest cost will be the global suffering. We increasingly realize just what a tremendous impact Parkinson's disease can have on quality of life, not only for affected individuals but also for their family, friends, and other acquaintances.

**MO: What evidence has emerged that multidisciplinary care is better for Parkinson's disease?**

**BB:** Most people who are diagnosed with Parkinson's disease will not receive the care they require. In fact, it is safe to say that care is far



Left to right:

Bastiaan R. Bloem, MD, PhD, FRCPE; Ray Dorsey, MD; Michael S. Okun, MD; Tanya Simuni, MD, FAAN.

from optimal for the large majority of people with Parkinson's in the world. This will result in avoidable disability and preventable costs for society.

**RD:** Treatment for Parkinson's disease rests on four pillars: appropriate medication, surgery in some instances, personal support to promote self-management, and a multidisciplinary team of health care providers.

**TS:** Most people do not receive all four pillars of treatment, and hardly any receive multidisciplinary care. In fact, even in highly developed countries such as the U.S., many patients do not even have access to a neurologist, let alone an expert in movement disorders.

**BB:** There are now several studies strongly supporting that multidisciplinary care is important for Parkinson's disease (*J Parkinsons Dis* 2020; 10:1087; *Mov Disord* 2020; 35:1509).

**MO:** How can we bring care into the home?

**RD:** In the setting of the Covid-19 pandemic, we saw a 100-fold increase in the use of telemedicine for older adults, including those with Parkinson's disease. This approach can bring Parkinson's care to patients instead of bringing patients to care (*Lancet Neurol* 2020; 19:623).

**BB:** The crisis has shown us that telemedicine can be delivered not only by a neurologist but also by physical therapists, nurses, social workers, psychologists, neurosurgeons, and nutritionists. This could be a game changer for providing

multidisciplinary care and for delivering it right where it is needed most: within the patient's own home.

**TS:** Telemedicine can also be used to conduct clinical research trials in the home setting, making research participation available to many more individuals.

**MO:** Telemedicine will soon be widely used to remotely adjust device-based therapies such as deep-brain stimulation (*Mov Disord* 2020; 35:909).

**MO:** Do you recommend exercise, and is exercise preventive for Parkinson's?

**TS:** There are clear benefits of exercise for those with Parkinson's, and I recommend it for all of my patients.

**RD:** Collectively, and based on the literature, most Parkinson's experts now recommend exercise as a first-line treatment. The evidence is strongest for aerobic exercise, and recent studies show that regular engagement in aerobic exercise helps to stabilize motor symptoms (*JAMA Neurol* 2018; 75:219; *Lancet Neurol* 2019; 18:998). And there is some preliminary work to suggest that aerobic exercise might even help to slow down the progressive course of Parkinson's disease; however, more studies are needed in this area.

**BB:** There is also an interest in exploring whether physical fitness could be important to preventing the later onset of Parkinson's disease. An analysis

of over 500,000 participants pooled from multiple studies revealed that the highest level of exercise was associated with a 21% decreased risk for developing Parkinson's compared with the lowest exercise level (*JAMA Netw Open* 2018; 1:e182421). Although promising, the protective effects of exercise are far from absolute (*Lancet Neurol* 2016; 15:1257). A recently launched study is expected to provide more definitive data specifically regarding the "dose" of exercise (NCT04284436).

**MO:** Should we be focused on symptomatic therapies, disease-modifying therapies, or cure therapies?

**TS:** This is a provocative question. I believe that we should focus on all areas. There are a million patients affected by this debilitating disease today in the U.S., and they deserve better symptomatic treatments. At the same time, all these people hope to witness the arrival of a cure for their disease. While such a cure is our ultimate goal, realistically we are not there yet, and we will not be able to set timelines until we have a full understanding of the disease biology.

**RD:** Our armamentarium is currently void of effective therapies for the advanced stages of the disease, including dopaminergic-resistant motor manifestations (falling, freezing, postural instability, dysphagia). In our quest for disease modification and cure, we cannot miss this area.

**BB:** We must not forget the spectrum of non-motor manifestations (including fatigue, sleep dysfunction, cognitive dysfunction) that may be important contributors to disease-related quality of life impairment, for which improved symptomatic treatments remain urgently needed.

**MO:** We are less likely to achieve a cure in the short term; however, the development of precision medicine-based therapies targeting specific genetic forms of Parkinson's disease may be on the horizon. It is quite conceivable that these precision approaches will allow us to slow down the course of Parkinson's disease within the foreseeable future.

**MO:** What is in the pipeline for pharmacological therapies?

**TS:** The pipeline is rich. A recent comprehensive review of experimental therapeutics cited 145 ac-

tive clinical trials that include symptomatic and disease-modifying treatments and span phase 1 (35%), phase 2 (46%), and phase 3 (19%) drug development (*J Parkinsons Dis* 2020; 10:757). In symptomatic pharmacotherapies, the most active programs are aimed at developing long-acting preparations of levodopa either via oral delivery or by subcutaneous levodopa infusions. There

are also novel molecules targeting pathways to improve cognition and to address falling.

**BB:** In addition to new drugs, there are also many promising nonpharmacological interventions that are being developed for providing symptomatic relief. Examples include games to support cognitive functioning and abdominal binders to treat orthostatic hypotension.

**RD:** We have spent tens of millions of dollars on potential disease-modifying therapeutics and to date have come up empty. The current generation of candidates are more grounded in disease biology and more informed by recent discoveries (genetics and molecular biology). Further, our ability to track disease progression has been enhanced by emerging biomarkers.

Data overwhelmingly support the use of levodopa rather than other levodopa-sparing strategies, perhaps even in the early stages of the disease.

**MO:** Many laboratories are studying neuroimmunology, neuroinflammation, nutritional therapies, and other out-of-the-box approaches.

**TS:** Two of the most active and interesting categories for disease modification include  $\alpha$ -synuclein and genetically targeted therapeutics.

**MO: What are some pearls for clinical practice in Parkinson's disease?**

**TS:** Treat symptoms that are bothersome for the person with Parkinson's and not just the symptoms visible to others. I aggressively address falling and other safety issues if they emerge.

**BB:** Data overwhelmingly support the use of levodopa rather than other levodopa-sparing strategies, perhaps even in the early stages of the disease. There is really no need to postpone symptomatic pharmacotherapy in patients

experiencing disability. Yet too many practitioners still suffer from "levodopa phobia" (*NPJ Parkinsons Dis* 2018; 4:31).

**RD:** Always assess and appropriately treat the nonmotor manifestations, which frequently impair quality of life more than the highly visible and recognizable motor symptoms. There are available and proven approaches to address sleep issues, depression, psychosis, and autonomic symptoms.

**MO:** Numerous studies have demonstrated the many benefits of deep-brain stimulation surgery, which has become part of standard Parkinson's care in many regions of the world. This therapy is excellent for tremor, dyskinesia, and on-off motor fluctuations but does not adequately address walking, talking, or cognitive issues.

## Topic Update

# Treatment of Acute Ischemic Stroke

Pooja Khatri, MD, MSc

Acute stroke care has evolved rapidly over the last 5 years, following a relatively quiescent 20 years since the approval of alteplase for stroke. Endovascular therapy (EVT) has proven to be one of the most impactful treatments in medicine in patients within 6 hours (and in selected patients up to 24 hours) from last known well (LKW). More recently, thrombolysis has been shown to benefit patients arriving to medical attention at 4.5 hours to 24 hours from LKW but conceivably within 4.5 hours of actual onset, and possibly in those with up to 9 hours of actual symptom duration. From the clinician's perspective, this sea change has required a rapid adaptation of systems of care and related protocols to ensure wide and consistent access to evidence-based treatments. The current state of this acute stroke care, with an eye toward future directions, is summarized below.

## Reperfusion Strategies for the Early Time Window

### INITIAL EMERGENT EVALUATION

Hallmarks of a well-oiled machine for acute stroke care typically include:

- Prenotification of the emergency department by prehospital providers
- Rapid triage of presumptive stroke patients from the ambulance to the computed tomography (CT) or magnetic resonance imaging (MRI) scanner
- Performance of both parenchymal (CT/MRI) and vascular assessments (CT angiography [CTA]/magnetic resonance angiography [MRA]) concurrently
- Activation of the stroke specialist before imaging results return
- Initiation of thrombolysis while the patient is in the scanner, before initiating vascular imaging

These best practices enable door-to-needle times for thrombolysis below 45 minutes, and door-to-EVT reperfusion times below 120 minutes (*Stroke* 2017; 48:A86; *Circ Cardiovasc Qual Outcomes* 2017; 10:e003227). Further time efficiencies have been created by smartphone-based applications that facilitate rapid view of neuroimaging. Once EVT eligibility is established, rapid transport of the patient

to a neuroangiography suite, with rapid mobilization of clinical staff, becomes paramount to optimizing clinical outcomes (*JAMA* 2016; 316:1279).

### THROMBOLYSIS CONSIDERATIONS IN THE EARLY TIME WINDOW

Upon review of parenchymal imaging, and ruling out intracranial hemorrhage, thrombolysis is the first consideration. The most common reasons that patients are ineligible for thrombolysis include deficits judged as nondisabling at the time of presentation, concurrent therapeutic anticoagulants, and recent major surgery. An important point for clinicians to understand is that early ischemic change on CT scan, in contrast to marked hypodensity, is not an absolute contraindication for alteplase (*JAMA* 2001; 286:2830).

Among thrombolytic agents, alteplase remains the only FDA-approved drug therapy for stroke, with guideline support up to 4.5 hours from the LKW time (*Stroke* 2019; 50:e344). Off-label tenecteplase is increasingly used due to ease of administration (bolus only) and growing empiric evidence to suggest comparable efficacy (*Stroke* 2020; 51:3440). Definitive data demonstrating noninferiority of tenecteplase to alteplase should be available in the near-term future (NCT03889249, NCT02814409). Adding adjunctive intravenous antithrombotics to improve reperfusion speed and success is also under investigation (NCT03735979).

### EVT CONSIDERATIONS IN THE EARLY TIME WINDOW

In parallel to administering a thrombolytic, the clinician must rapidly review the vascular imaging for large vessel occlusion (LVO). Common exclusions for EVT include extensive early ischemic changes on CT scan (quantified as an ASPECTS score <6) and lower stroke severity based on examination (quantified as NIHSS score <6). Ongoing trials are testing whether these patients may also benefit from EVT (NCT03805308, NCT04167527, NCT03094715, NCT03796468).

## Reperfusion Strategies for the Extended Time Window

In the extended time window, advanced imaging is needed to support reperfusion therapy decisions.

### IMAGING FOR PATIENTS WITH LVOS AND POTENTIALLY EVT-ELIGIBLE

For stroke patients with LVO on CTA within 6 to 24 hours from LKW, either CT perfusion (CTP) or MR perfusion-weighted imaging (MR-PWI), along with automated postprocessing, is the next step. Despite the opportunity to treat these patients later than previously possible, rapid evaluation remains vital, as fewer patients will become eligible by these criteria as time goes on. Automated software has not been consistently available at all primary stroke centers in the U.S., and patients presenting at these centers may require urgent transfer to a software-resourced center when possible.

### IMAGING CONSIDERATIONS FOR PATIENTS NOT EVT-ELIGIBLE AND POTENTIALLY THROMBOLYSIS-ELIGIBLE

Among patients within 4.5 to 24 hours from LKW and without an LVO, a subset will have unwitnessed onset and be within 4.5 hours of symptom *recognition*. MRI can be used as a surrogate for LKW for these patients when emergently available. Patients with evidence of acute ischemic stroke on diffusion-weighted imaging (DWI) without marked hyperintensity on fluid-attenuated inversion recovery (FLAIR) show benefit from alteplase comparable with that seen for patients receiving alteplase within 4.5 hours of LKW (*N Engl J Med* 2018; 379:611). The benefit of alteplase among the 22% of participants who had small (<2 cm) strokes was remarkably similar to the benefit observed in the overall cohort in the pivotal trial (*JAMA Neurol* 2019; 76:641). These data dispelled the notion of differential thrombolytic treatment effects based on stroke etiology. Of note, the trial included approximately 20% of patients who would now qualify for EVT, and the concurrent role of thrombolysis and EVT for this group has not been defined.

For the subset of patients with *witnessed* onset from 4.5 to 9 hours of LKW and no LVO, penumbral imaging-based selection of patients for thrombolysis appears promising. This is based on the recent phase 3 EXTEND trial (*N Engl J Med* 2019; 380:1795), in which 35% of trial participants had symptom duration beyond 4.5 hours, and a related pooled analysis including two prior trials that missed their primary endpoints (*Lancet* 2019; 394:139); however, the quality of this evidence is low (*Eur Stroke J* 2021 Feb 19

[e-pub]; DOI:10.1177/2396987321989865), and the findings would benefit from confirmation.

About 70% of EXTEND participants harbored LVOs and would now be treated with EVT. This is not surprising, as mismatch on perfusion imaging has been shown to be less common in smaller strokes. Combining thrombolysis with EVT in the extended time window among patients with favorable perfusion profiles is under study in ongoing trials (NCT03785678, NCT04454788). Beyond 9 hours of symptom duration, randomized data aimed at testing thrombolysis have not been published.

### OVERALL STRATEGY FOR ADVANCED IMAGING

Imaging strategies for patients who present to emergency departments from 4.5 to 24 hours from LKW after the prerequisite CT/MRI and CTA/MRA are all imperfect. The most appealing approach for stroke care is to obtain all of the necessary information up front with an initial MRI, including MRI-PWI and MRA, although this may not be feasible at many stroke centers and some patients may have contraindications to MRI. A staged approach — CTP for patients with LVO or those who cannot obtain MRI, and MRI for those without LVO and able to receive it rapidly — may be the next best option to identify the most patients eligible for reperfusion therapies. Current evidence suggests that MRI DWI-FLAIR mismatch will identify more, although not all, thrombolysis-eligible patients compared with perfusion imaging; it may double the detection of patients with unknown timing of symptom onset (*Stroke* 2021; 52:373).

### Summary

The treatment opportunities for acute ischemic stroke patients have rapidly expanded over the last 5 years. Many ongoing trials promise continued rapid advancement toward new and cohesive treatment options.

#### Pooja Khatri, MD, MSc

Dr. Khatri is Professor of Neurology, Director of the Vascular Neurology Division, and Director of the UC Stroke Team, University of Cincinnati; and Co-Director of the NIH StrokeNet National Coordinating Center.



## Topic Update

# Migraine Treatments: Integrating New Therapies and the Path Forward

Teshamae Monteith, MD, FAHS, FAAN

Migraine is a chronic disorder with episodic manifestations characterized by disabling headache, gastrointestinal symptoms, sensory disturbances, and a host of other neurological symptoms. There has been a paucity of research to advance migraine despite the fact that it affects one billion people worldwide and is the number one cause of disability in individuals under 50 years of age.

Well-designed clinical trials are crucial to evaluate migraine treatments given the lack of available biomarkers to guide therapeutic development. The introduction of multiple target-specific molecules as well as the emergence of new guidelines for controlled trials are available to improve methods for preventive and active drug development (*Cephalalgia* 2020; 40:1026). Suggested primary endpoints for the more-recent trials have shifted to the change from baseline in migraine days and moderate-to-severe headache days. Another shift has been the use of a 50% responder rate for the reduction of migraine days. Still lacking are patient samples with better representation of ethnic/racial diversity, medication overuse, and histories of multiple preventive drug failures. Since new therapies have recently emerged, older ones with suboptimal outcomes and high adverse event profiles are falling out of favor. A review of these recent therapeutic advances follows.

## Looking Back at OnabotulinumtoxinA — 10 Years of Use

Prior to the approval of onabotulinumtoxinA for chronic migraine, the oral drug topiramate had the best evidence for this indication. The FORWARD study showed that onabotulinumtoxinA had greater clinical utility than topiramate (*Headache* 2019; 59:1700). The difference was mostly driven by tolerability issues associated with topiramate in addition to a relatively higher number of onabotulinumtoxinA patients remaining on treatment. In 2019, a meta-analysis confirmed the long-term safety and efficacy of onabotulinumtoxinA injections when administered every 12 weeks (*Cephalalgia* 2019; 39:945). Early

onset of headache effect may be observed for headache and migraine days in onabotulinumtoxinA responders with onset beginning 1 week following the first injection.

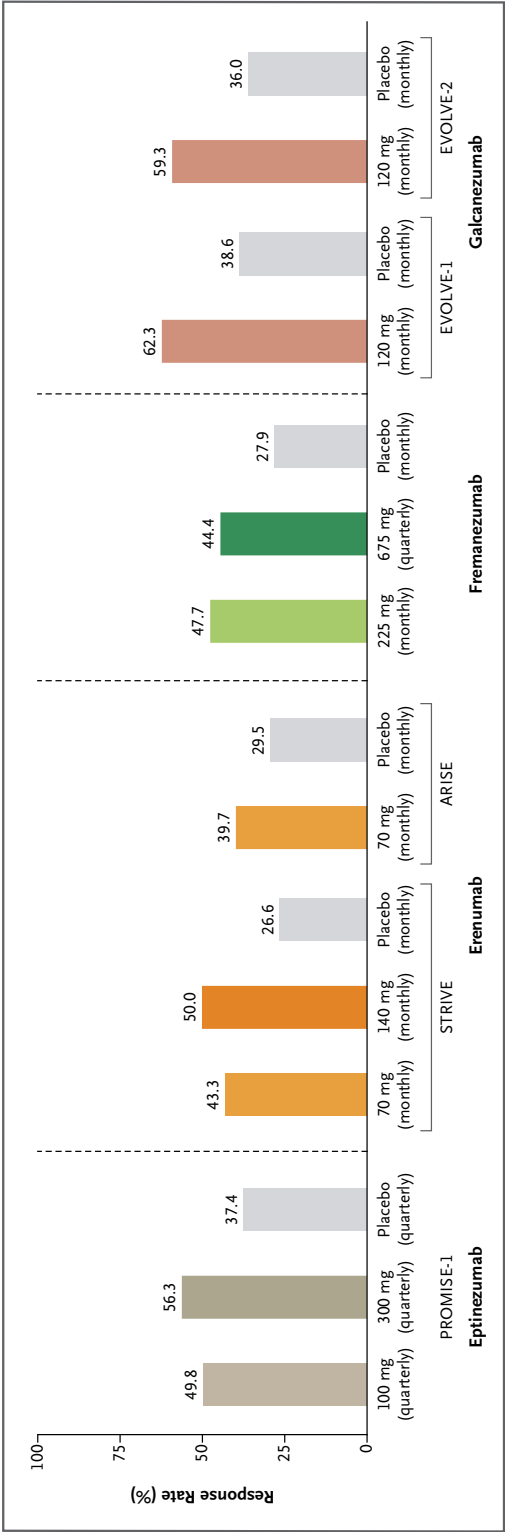
## CGRP Monoclonal Antibodies for Migraine Prevention

To date, there are four monoclonal antibodies to the calcitonin gene-related peptide (CGRP) or its receptor for prevention of episodic and chronic migraine (see figure). Long-term open-label studies continue to show high responder rates of 50% to 75%, tolerability, cumulative and sustained functional benefits, and efficacy in those who previously failed multiple preventives and those with medication overuse. Tolerability remains a major benefit of this treatment class and is limited most commonly by injection site reactions accompanying subcutaneous administration and hypersensitivity reactions. An American Headache Society position statement cites the cost considerations, including the initial trials of older drugs such as topiramate, divalproex, the beta-blockers, tricyclic antidepressants, or serotonin-norepinephrine reuptake inhibitors (*Headache* 2019; 59:1). However, the major benefits of newer anti-CGRP monoclonal antibodies are that they do not require dose escalation, offer rapid onset of therapeutic benefits, and have no drug-drug interactions and favorable tolerability profiles. Most importantly, long-term efficacy and safety has been established for episodic and chronic migraine.

## Novel Specific Acute Migraine Therapies

Much progress has been made in the development of novel therapeutics for acute migraine management since the introduction of triptans in the 1990s. A recent trend in acute migraine therapies has been the emergence of specific acute treatments with better tolerability. Unlike triptans, which bind to serotonin 1B, 1D, and 1F subtypes, lasmiditan was the first 5HT<sub>1F</sub> agonist, known as a “ditan,” to receive FDA approval for acute treatment of migraine (*Neurology* 2018; 91:e2222). Benefits of the ditans include no association with any vasoconstriction

### Response Rates in Phase 3 Randomized Trials of Monoclonal Antibodies against CGRP or Its Receptor for Prevention of Episodic Migraine



The response rate was defined as the proportion of patients with a 50% reduction in the number of migraine days per month during the study period.  
Adapted from Ashina M. *N Engl J Med* 2020; 383:1866.

and possible effectiveness even in triptan non-responders. Similarly, CGRP antagonists, the gepants, also do not result in any vasoconstriction and have no contraindication in patients with vascular disease. In clinical trials, rimegepant and ubrogepant were both shown efficacious in achieving greater freedom from headache pain and absence of the most bothersome pain symptom at 2 hours postdose compared with placebo (*JAMA* 2020; 324:890; *Headache* 2020; 60:686). The benefits of the gepants include a relatively benign safety profile; the most common adverse effect is nausea, occurring in about 2% to 3%. Interestingly, preliminary studies suggest that the gepants, notably atogepant, may be useful for migraine prevention (*Lancet Neurol* 2020; 19:727). These emerging CGRP antagonism data have blurred the distinction between acute and preventive indications for migraine. Finally, we are seeing new ways of administering old drugs with novel delivery methods. One example is an olfactory delivery technology used to administer dihydroergotamine to the nasal space (*Headache* 2019; 59:394), which is currently under FDA review.

### What's New in Neuromodulation

There are currently three available neuromodulatory devices FDA approved for migraine. The first wearable FDA-approved device, known as Cefaly Dual, is thought to work by using external stimulation of the trigeminal nerve. The gammaCore device targets the vagus nerve for treatment of acute migraine attacks, and possibly for prevention. A more recent alternative for acute migraine attacks is a remote electrical neuromodulation device (Nerivio; TheraNica), which stimulates the upper-arm peripheral nerves to induce conditioned pain modulation (*Headache* 2019; 59:1240). It uses an analgesic mechanism in which conditioning stimulation inhibits pain in remote body

regions, such as the head. The device is thought to work by activation of the descending pain inhibition pathways, which pass through the brainstem pain regulation center (periaqueductal gray, rostral ventromedial medulla, subnucleus reticularis dorsalis) and are part of the pathway leading to the release of the neurotransmitters serotonin and noradrenalin, which inhibit incoming pain signaling in the trigeminal cervical complex. During the clinical trial, pain relief at 2 and 48 hours, and freedom from the most bothersome symptom at 2 hours post-treatment was significantly greater with the active treatment compared with the sham treatment.

### Practice Recommendations

Migraine has been increasingly recognized as a heterogeneous disease in its clinical presentation, physiological characteristics, and response(s) to therapies. Many sufferers have endured suboptimal outcomes, which makes the transformational movement toward targeted therapies and expanded options exciting. Lifestyle modifications, such as sleep hygiene, physical activity, diet and mindfulness, should all be considered for integration with the newer drug and device therapies. The future of migraine therapy will likely continue to be an individualized, integrated approach.

#### Teshamae Monteith, MD, FAHS, FAAN

Dr. Monteith is Associate Professor of Clinical Neurology and Chief of the Headache Division at the University of Miami, Miller School of Medicine.



## Topic Update

# Long-Term Neurological and Neuropsychiatric Effects of Covid-19

**Tom Solomon, FRCP, PhD**

**Benedict Michael, MRCP, PhD**

**Tim R. Nicholson, MD, PhD**

As the Covid-19 pandemic has progressed, the two most commonly reported acute neurological syndromes associated with the infection in hospitalized patients have been stroke and encephalopathy, the latter frequently manifesting as delirium (*Lancet* 2020; 19:767). In addition, a range of chronic neurological and neuropsychiatric and other symptoms have been reported in both hospitalized and non-hospitalized patients. Since May 2020, newly formed patient groups have described this as “long Covid” or “Covid long-hauler syndrome,” in pioneering research and advocacy.

## What is Long Covid?

There is as yet no universally agreed definition for long Covid. The U.K. National Institute for Health and Care Excellence (NICE) has defined “ongoing symptomatic Covid-19” as symptoms beyond 4 weeks and “post-Covid-19 syndrome” beyond 12 weeks. The U.S. Centers for Disease Control and Prevention (CDC) has also recognized the importance of symptoms beyond 4 weeks. Both organizations acknowledge the term “long Covid” but do not specifically define it (*JAMA* 2020; 324:2251; NICE guideline; 2020 Dec 18; [NG188]).

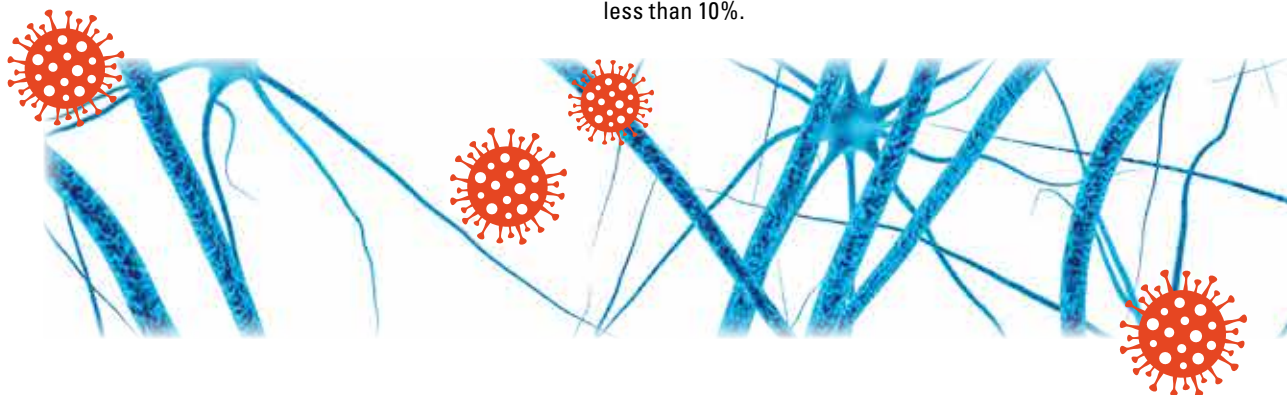
From a neurological perspective, the long-term effects of Covid-19 can be considered as:

- Sequelae of identified neurological complication(s) of acute infection, e.g., a stroke
- Known consequences of prolonged hospitalization with severe Covid-19, e.g., critical neuropathy or cognitive impairment following intensive care
- Heterogenous combinations of neurological, neuropsychiatric, and multisystem symptoms, which frequently occur in patients who had milder Covid-19 initially; there may be similarities to postviral fatigue or chronic fatigue syndrome

There is concern among advocacy organizations that some long Covid patients are not taken seriously and struggle to access care.

## Long-Term Symptoms

There is a paucity of high-quality data on the symptoms of long Covid. This is partly due to a lack of case definitions and the conflation of subtypes. A non-peer-reviewed meta-analysis pooling information from 15 studies of mostly hospitalized patients analysed data from 47,910 individuals (medRxiv 2021 Jan 27; [21250617, preprint]). Long-term symptoms were reported in 80% of Covid patients, and there were 55 individual long-term symptoms. The seven most common symptoms were fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), dyspnea (24%), ageusia (23%), and anosmia (21%). Subjective memory loss, hearing loss or tinnitus, anxiety, depression, pain, and sleep disorder occurred in 10% to 20%. Health care-related mental health and psychiatric illness were reported in less than 10%.



In a non–peer-reviewed patient-led online survey of 3,762 people from 56 countries, 92% of whom were not hospitalized, the most frequent symptoms were fatigue (78%), postexertional malaise (72%), and cognitive dysfunction (55%; medRxiv 2020 Dec 24; [20248802, preprint]). Many survivors of Covid-19 report “brain fog” and describe difficulty thinking clearly, mental fuzziness, poor memory, and fatigue. Cognitive impairment is common anyway among survivors of prolonged intensive care. However, a non–peer-reviewed study of 84,285 people in the U.K. who had recovered from suspected or confirmed Covid-19 (including many nonhospitalized patients) reported poor performance across multiple cognitive domains (medRxiv 2020 Oct 20; [20215863, preprint]).

### Risk Factors

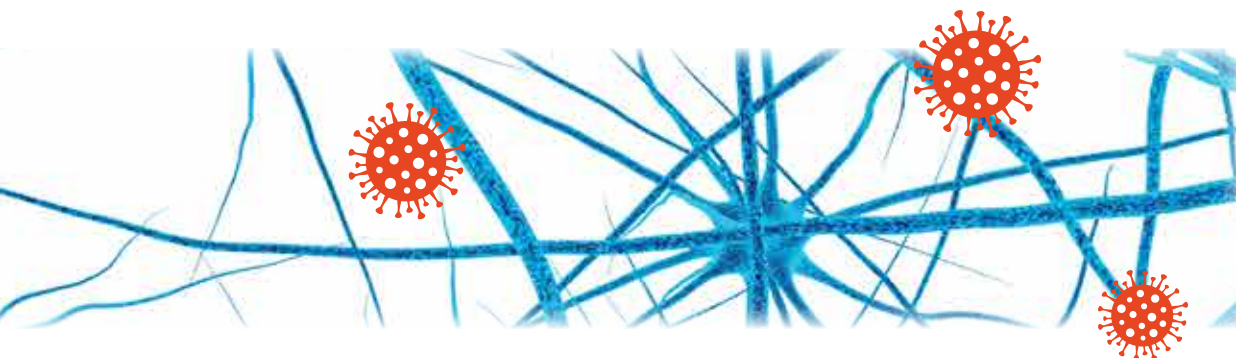
Many neurological and neuropsychiatric symptoms are common even in those who experienced a mild Covid-19 illness initially. In a study of 128 patients (71 inpatients and 57 outpatients) in Ireland, 67 (52%) reported ongoing fatigue at a median 10 weeks after admission (*PLoS One* 2020; 15:e0240784). Fatigue was more common in females and those with a history of anxiety or depression and was similarly likely to occur in those with mild versus more-severe Covid-19 disease. Another study suggests that younger people may be especially likely to develop long Covid: Among 126 Covid-19 patients postdischarge, clinically significant symptoms of stress response, anxiety, and depression were found in 39 (31%), 28 (22%), and 48 (38%) patients, respectively; these symptoms were most pronounced in those under 60 (*Am J Geriatr Psychiatry* 2020; 28:1030).

### Disease Mechanisms

Severe brain disease as a result of Covid-19 is likely due to a combination of inflammatory, ischemic,

and other disease mechanisms (*Nat Rev Neurol* 2021 Feb; 17:65). However, the extent to which these processes contribute to the more subtle neuropsychiatric manifestations of Covid-19 is unclear. Research suggests that some patients with prolonged symptoms after Covid-19 have an exaggerated and ongoing systemic inflammatory response. One study investigated 384 hospitalised Covid-19 patients, a median of 54 days after discharge, who had fatigue (69%), breathlessness (53%), cough (34%), and depression (15%). In this cohort there was elevated D-dimer in 30%, elevated CRP in 10% and lymphopenia in 7% (*Thorax* 2020 Nov 10; [e-pub]; DOI: 10.1136/thoraxjnl-2020-215818). However, another Covid-19 fatigue study in Ireland found no elevation of inflammatory markers (*PLoS One* 2020; 15:e0240784).

Imaging studies may be a vehicle to reveal potentially pathogenic mechanisms. One such study examined 58 patients postdischarge, one third from intensive care, of whom 32 (55%) had fatigue and 16 (28%) had impaired cognitive performance (*EClinicalMedicine* 2021; 31:100683). Compared with controls, at 8 to 12 weeks after acute illness, there were changes in the thalamus, posterior thalamic radiations, and sagittal stratum on T2-FLAIR MRI imaging. Another study in 37 patients showed abnormalities in the medial temporal lobe, nonconfluent multifocal white matter hyperintense lesions, with associated hemorrhagic, and extensive and isolated white matter microhemorrhages (*Radiology* 2020; 297:E242). Further, an FDG-PET imaging case-control study of 35 intensive care Covid-19 patients revealed cognitive impairment as well as hypometabolism in the olfactory gyrus, limbic and paralimbic regions (*Eur J Nucl Med Mol Imaging* 2021 Jan 26; [e-pub]; DOI: 10.1007/s00259-021-05215-4). The degree of hypometabolism was interestingly associated with the number of functional complaints.



## Management and Future Directions

There are no universally accepted recommendations for the treatment of persistent neurological and neuropsychiatric symptoms following acute Covid-19. Headaches, fatigue, and other common complications are managed similar to standard clinical practice. A recent UK guideline emphasises a holistic approach integrating physical, psychological, and psychiatric aspects of rehabilitation through “one-stop” clinics (*BMJ* 2021; 372:n136). Self-management using symptom diaries and tracking phone apps has also been suggested. Covid-19 support groups are also proving useful. For patients who had severe Covid-19, many ongoing symptoms after discharge are similar to those following other serious illnesses and can be addressed as such. Going forward, we propose “long Covid” be reserved for those who had initial relatively mild (i.e., nonhospitalized) Covid-19 but have ongoing symptoms; this aligns with original descriptions from patient groups. For these patients, a precise case definition and case-control studies using objective measures wherever possible will improve understanding of the risks and disease mechanisms. This may also help our understanding of postviral symptoms and chronic fatigue syndrome more widely.

### Tom Solomon, FRCP, PhD

Dr. Solomon is Professor of Neurology, Walton Centre NHS Foundation Trust and University of Liverpool, and Director, NIHR Health Protection Research Unit in Emerging and Zoonotic Infections, University of Liverpool.



### Benedict Michael, MRCP, PhD

Dr. Michael is a Senior Clinician Scientist Fellow at the Institute of Infection, Veterinary and Ecological Sciences at the University of Liverpool and an Honorary Consultant Neurologist at the Walton Centre NHS Foundation Trust.



### Tim R. Nicholson, MD, PhD

Dr. Nicholson is an Honorary Consultant Neuropsychiatrist at the South London and Maudsley Hospital NHS Foundation Trust and Senior Clinical Lecturer at the Institute of Psychiatry, Psychology & Neuroscience, King's College London.



## Topic Update

# Treatment of Multiple Sclerosis

**Bianca Weinstock-Guttman, MD**

**Dejan Jakimovski MD, PhD**

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS). In the majority of patients, disease onset is characterized by intermittent episodes of neurological worsening followed by a full or partial recovery related to its inflammatory/demyelinating aspect, whereas a more neurodegenerative component dominates in the later stage (*N Engl J Med* 2018; 378:169). Most persons with MS (pwMS) exhibit their first symptoms in early adult life (ages 20–50 years) (*N Engl J Med* 2018; 378:169). After an average disease duration of 10 to 20 years, patients transition into a progressive phase of the disease with a continuous accumulation of disability (*N Engl J Med* 2018; 378:169).

The successful implementation of potent anti-inflammatory, disease-modifying treatments (DMTs) and better overall MS care have significantly improved disability outcomes and longevity (*Nat Rev Neurol* 2019; 15:329). In this update, we present an overview of current and future pharmacological treatments for MS, with a focus on recent and upcoming drug developments.

## B-Cell Depletion and S1PR Modulators

Over the past few years, the field of MS pharmacotherapy has observed several innovations, including first-time approval of DMTs for treatment of primary progressive MS (PPMS) and active secondary progressive MS (SPMS). In the pivotal phase 3 PPMS ORATORIO trial, treatment with ocrelizumab (humanized anti-CD20 antibody for B-cell depletion) resulted in a significant 24% reduction in disability progression compared with placebo (*N Engl J Med* 2017; 376:209). Similarly, siponimod (a second-generation oral sphingosine-1-phosphate receptor [S1PR] modulator) for SPMS resulted in a significant 21% reduction in disability worsening and a 55% decrease in annualized relapse rate compared with placebo (*Lancet* 2018; 391:1263). Similar second-generation S1PRs (ozanimod and ponesimod) had positive phase 3 trials and were either approved

or have been pending FDA approval (*Lancet Neurol* 2019; 18:1021). The new S1PR modulators have more-selective pharmacodynamic properties (S1PR1 and S1PR5 for siponimod; S1PR1 for ponesimod) and may also limit cardiovascular off-target effects through activation of S1PR3. These advances in therapy development have resulted in a significantly better cardiovascular safety profile as compared with the first-generation predecessor (fingolimod). A newer approach with potentially improved blood–brain barrier (BBB) permeation with advantageous effects on glial cells has been investigated in newer, more-selective products.

## Diroximel Fumarate

In late 2019, the FDA approved the use of diroximel fumarate (bioequivalent to dimethyl fumarate) for use in clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), and active SPMS. Compared with its predecessor, diroximel fumarate is more quickly metabolized into monomethyl fumarate and has shown a significantly lower incidence of gastrointestinal adverse events and drug discontinuation due to adverse events (*CNS Drugs* 2020; 34:185). Lastly, based on two parallel, phase 3 trials (ASCLEPIOS I and II), a fully human anti-CD20 antibody medication ofatumumab was recently approved for treatment of relapsing forms of MS, with improved convenience of self-administration compared with other infusion-based B-cell–depleting therapies (*N Engl J Med* 2020; 383:546).

## Bruton's Tyrosine Kinase Inhibitors

Future introduction of Bruton's tyrosine kinase inhibitors (BTKis) is another step toward improving efficacy and safety of MS treatment. BTKis provide reversible suppression of the homonymous kinase, which is the main downstream signaling enzyme in B-cells and in microglia. Compared with antibody B-cell depletion, BTKis can readily cross the BBB and inhibit the resident and compartmentalized inflammatory cells. With a half-life of 2 hours, a BTKi can be practically and easily initiated, discontinued, and/or re-initiated if necessary. This will allow better management of possible adverse events compared

with the long-lasting immunosuppression that is antibody-dependent B-cell depletion. There are currently four different BTKs in development — fenebrutinib, evobrutinib, tolebrutinib, and BIIB091 — with some large, phase 3 RRMS and PPMS trials currently recruiting patients. Another selective TK inhibitor, masitinib, was also able to reduce disability progression in a mixed cohort of patients with PPMS and SPMS (37% relative reduction vs. placebo; NCT01433497).

### Other Drugs in Development

The future MS drug pipeline includes pharmacological approaches targeting distinct pathways hindering MS pathobiology, such as the immune tolerance—inducing ATX-MS-1467 (peptide mixture of four different myelin basic protein epitopes), temelimab (antibody towards the MS-associated retrovirus envelop protein), and repair interventions such as elezanumab (antibody towards repulsive guidance molecule A).

### Additional Treatment Considerations in 2021

Because of the shifting focus on the benefit of early DMT initiation after diagnosis, clinicians are increasingly developing a personalized risk-benefit analysis of two main but opposing treatment paradigms. Traditionally employed has been the “escalation concept” that entails the initial use of first-line, safer-but-less-efficacious treatments, which can be followed by switching to second-line, more-potent medications. This switch may be necessitated if, for example, a disease breakthrough occurs. Alternatively, the “induction paradigm” includes early use of highly potent treatment (HPT). Accumulating observational data currently favor early treatment and use of early HPT interventions that may induce long-term disease stability (*JAMA Neurol* 2019; 76:536). Further direction might be provided by two currently ongoing studies (DELIVER-MS; NCT03535298 and TREAT-MS; NCT03500328) that randomize pwMS to early use of HPT (alemtuzumab, ocrelizumab, natalizumab) or

to an escalation arm (IFN- $\beta$ , glatiramer acetate, or oral medication).

Aging of pwMS has significant implications regarding the risk-benefit analysis and long-term DMT use in older pwMS (*Expert Opin Drug Saf* 2020; 19:1121). Age-induced immunosenescence in MS cohorts will contribute to a greater risk for common and serious infections, including herpetic infections and progressive multifocal leukoencephalopathy (*Mult Scler* 2020:1352458520964778). Moreover, age-based

Age-based changes in MS pathophysiology are thought to significantly reduce the effectiveness of currently available disease-modifying therapies.

changes in MS pathophysiology are thought to significantly reduce the effectiveness of currently available DMTs. Age subgroup analysis of most regulatory phase 3 trials and trial meta-analyses suggest lower or non-significant DMT efficacy in pwMS older than 40 years (*Front Neurol* 2017; 8:577). Consequently, recent studies have explored the effect of DMT discontinuation and have reported conflicting results ranging from no signs of disease re-activation to discontinuation-

induced disability worsening (*Continuum [Minneapolis]* 2019; 25:715). An ongoing large DMT discontinuation study in pwMS (DISCO-MS; NCT03073603) may provide further clarification for this area of care.

Finally, treatment decisions have been significantly impacted by the emergence of the SARS-CoV-2 pandemic and the distribution of SARS-CoV-2 vaccines. Based on multiple national and international data registries, pwMS inherently do not have greater risk for contracting Covid-19 and do not have worse disease outcomes compared with the general population (*J Neurol Neurosurg Psychiatry* 2021; 92:107). Recent data derived from a global Covid-19 MS initiative has indicated that the use of B-cell-depleting therapy may potentially increase the risk for worse Covid-19 outcomes. These findings are not always observed, especially when considering different MS cohorts (*Ann Neurol* 2021 Jan 21; [e-pub] and *JAMA Neurol* 2020; 77:1079). There has been emerging evidence of attenuated vaccine response in pwMS treated with DMTs (other than IFN- $\beta$ ), especially in

those receiving B-cell-depleting therapy (*Mult Scler* 2014; 20:1074 and *Neurology* 2020; 95:e1999). Overall, the recently published vaccination practice guidelines from the American Academy of Neurology regarding non-Covid-related vaccines we would suggest should apply to SARS-CoV-2 vaccination and should guide MS care providers in creating ideal conditions for safe and efficacious vaccination (*Neurology* 2019; 93:584).

**Bianca Weinstock-Guttman, MD**



Dr. Weinstock-Guttman is Professor of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, and Director, Jacobs Multiple Sclerosis Center for Treatment and Research, Buffalo, NY.

**Dejan Jakimovski, MD, PhD**



Dr. Jakimovski is Research Assistant Professor, Buffalo Neuroimaging Analysis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York.

## Topic Update

# From Concussion to Chronic Traumatic Encephalopathy: Acute Management and Emerging Roles for Biomarkers

Breton M. Asken, PhD, ATC

Michael S. Jaffee, MD, FAAN

Concerted attempts to improve management of concussion or mild traumatic brain injury (mTBI) and to characterize long-term neurologic risks continue to spark unprecedented clinical research. Following acute concussion/mTBI, physical and cognitive exertion protocols should now be the norm, especially in the sports settings. Blood-based biomarkers have begun to revolutionize brain injury management, though the field in general remains nascent. Validating biomarkers capable of detecting neurodegenerative processes associated with head trauma, such as chronic traumatic encephalopathy (CTE), will be critical for differential diagnosis, refining clinical criteria, and for developing treatments. In this article, we provide an overview of the latest developments in these areas.

## Earlier, Active Treatment: Not Too Much, Not Too Little

Not long ago, concussed athletes frequently resumed sports participation either the same day as their injury or almost immediately following symptom resolution. Nonathlete mTBI management and some sports concussion settings can frequently occupy the other end of the spectrum as providers routinely have prescribed complete and extended rest or “cocoon” therapy. A paradigm shift toward stepwise physical and cognitive exertion has resulted in improved recovery outcomes (e.g., *JAMA Pediatr* 2019; 173:319) and has contributed to a marked drop in repeat sports concussion diagnoses within the same season (*Br J Sports Med* 2020; 54:102). Before allowing full activity clearance, sports protocols typically require an initial period (24–48 hours) of symptom-limited *relative* rest followed by increasingly intense aerobic and anaerobic activities without symptoms reemerging (*Br J Sports Med* 2017; 51:838). Similar protocols exist for returning to school or work and may be readily adapted to nonathletes. Nonathlete mTBI patients less frequently receive ongoing medical oversight; however, with the

expansion of multidisciplinary concussion clinics this option should be considered.

## Blood Biomarkers: Emerging Clinical Utility

Blood-based biomarkers measuring brain injury pathophysiology are knocking at the clinical doorstep. Among the most commonly studied concussion/mTBI biomarkers are glial fibrillary acidic protein (GFAP; astrocytic dysfunction), ubiquitin C-terminal hydrolase L1 (UCH-L1; ubiquitin proteasome pathway activity), neurofilament light (NfL; axonal injury), and total tau (axonal injury). In 2018, the U.S. FDA approved use of GFAP and UCH-L1 for acute mTBI management. Specifically, when measured <12 hours after injury in adults, a negative GFAP and UCH-L1 test effectively has excluded the need for a computed tomography (CT) scan mainly due to exceedingly low probability of intracranial lesion (*Lancet Neurol* 2018; 17:782). The clinical reality for the use of this test gained further traction in January 2021 following FDA approval of the first handheld, point-of-care device capable of rapid GFAP and UCH-L1 measurement.

A *diagnostic* blood-based biomarker for concussion remains an elusive holy grail. Some, but not all, studies have observed that acute postconcussion GFAP, UCH-L1, and total tau levels elevate from baseline and can differentiate concussion patients from asymptomatic controls (*JAMA Netw Open* 2020; 3:e1919771). Levels of similar acute-phase proteins occasionally can be associated with the duration of clinical symptoms and may possibly remain elevated chronically following concussion in a subset of patients. Inconsistencies across studies stem in part from the complex temporal dynamics of the brain’s response to injury. It is likely that specific proteins will have different diagnostic or prognostic utility depending on the injury severity and the time since the injury.

## CTE: Still Searching for Biomarkers

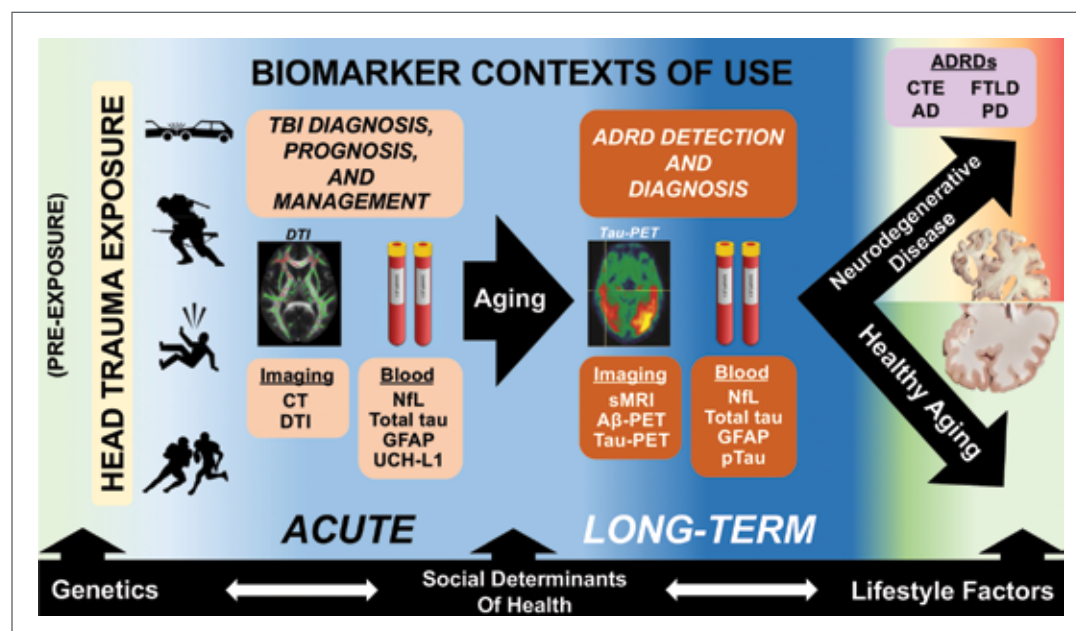
Head trauma is a recognized risk factor for later-life neurodegenerative disease, and the global population is aging rapidly (*Lancet Neurol* 2020; 396:413). Among neurodegenerative diseases, CTE

is the one most closely linked to head trauma, with patients usually having sustained many symptomatic (i.e., concussions/mTBIs) and asymptomatic (sub-concussive) head blows. Known high-risk patients include former collision sports athletes and military veterans, but others like intimate partner violence survivors may also be at risk. CTE prevalence, incidence, and other risk factors (beyond head trauma) are largely unknown.

CTE is diagnosable only by autopsy based on the pathognomonic lesion: perivascular accumulation

of hyperphosphorylated tau in neurons and astrocytes at the depths of cortical sulci. CTE tau shares many structural features with Alzheimer's disease (AD) tau, which elicited hope that well-validated AD biomarkers would prove useful for diagnosing CTE in living patients (e.g., positron emission tomography [PET] imaging of tau). Unfortunately, the excitement has diminished.

The tau PET tracer flortaucipir (FTP) was recently approved by the FDA for differential diagnosis of suspected AD but explicitly is *not* indicated for



**Figure:** Conceptual framework for the roles of biomarkers in the acute and long-term management of individuals with lifetime head trauma exposure. In research settings, DTI has advanced our understanding of TBI white matter pathophysiology. Structural MRI has limited use in acute head trauma but later in life can show atrophy patterns reflecting neurodegenerative disease or macroscopic evidence of prior trauma (e.g., cavum septum pellucidum). Blood biomarkers like NFL, GFAP, and total tau that elevate acutely after trauma also show promise in the detection of ADRDs. Other fluid biomarkers have potential for acute TBI diagnosis and management (e.g., alpha-2 spectrin breakdown products) as well as uncovering mechanisms linking prior trauma to neurodegenerative processes (e.g., inflammatory proteins, markers of blood-brain-barrier dysfunction). Phosphorylated tau biomarkers (pTau181, pTau217) appear highly specific to AD pathology, and PET is diagnostic for AD via FDA-approved radiotracers for Aβ plaques and AD tau tangles. Other tau tracers are being developed and studied in patients considered high-risk for CTE (e.g., MK-6240). Fluid biomarkers and PET neuroimaging may ultimately help identify head trauma-exposed individuals at highest risk for ADRDs as they age. This will inform how variations in genetics, social determinants of health, and lifestyle factors interact with head trauma exposure to positively or negatively impact brain health over time.

**Abbreviations:** Aβ — beta-amyloid; ADRD — Alzheimer's disease and related dementias; CT — computed tomography; CTE — chronic traumatic encephalopathy; DTI — diffusion tensor imaging; FTL — frontotemporal lobar degeneration; GFAP — glial fibrillary acidic protein; NFL — neurofilament light; PD — Parkinson's disease; PET — positron emission tomography; pTau — phosphorylated tau; sMRI — structural magnetic resonance imaging; TBI — traumatic brain injury; UCH-L1 — ubiquitin c-terminal hydrolase L1

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CTE diagnosis. In a 2019 study, former professional American football players had higher FTP signal than controls (*N Engl J Med* 2019; 380:1716). However, subsequent work has revealed that FTP most strongly binds late-stage AD tau pathology and may actually have low sensitivity to CTE tau and may lack a clear binding pattern (*Brain* 2020; 143:3477 and *JAMA Neurol* 2020; 77:517). Other tau PET tracers are now being studied.

### CTE in the Clinic: Keep a Broad Differential

There is no prototypical CTE clinical syndrome that has been defined; however, proposed criteria are under development (i.e., traumatic encephalopathy syndrome, or TES). Patients may present with cognitive, behavioral, and/or motor changes that are difficult to distinguish from other neurodegenerative syndromes. Most brains with CTE also exhibit non-CTE pathologies that likely contribute to clinical symptom expression. Thus, we conclude that clinicians should have a broad differential. While CTE appears highly specific to prior repetitive head trauma, such trauma is associated with increased risk of multiple other neurodegenerative pathologies (e.g., AD, TDP-43 proteinopathies, synucleinopathies) with or without co-occurring CTE. Clinically available AD biomarkers (PET, cerebrospinal fluid) may still be useful for *ruling out* AD and for raising suspicion for CTE in head trauma-exposed patients with ambiguous clinical syndromes.

### Ongoing and Future Research

Current concussion/mTBI treatment protocols are symptom-guided, however importantly physiologic dysregulation outlasts clinical symptom expression. Biomarkers offer the opportunity for tracking *biologic* recovery in a more precise manner. Relatedly, highly variable concussion/mTBI symptom presentations have sparked interest in classifying distinct syndrome subtypes. Analogous approaches to defining biologic

subtypes may help to identify patients at risk for (or alternatively resilient against) poor neurologic outcomes.

Biomarkers will be key for identifying aging patients at risk for neurodegenerative diseases like CTE and accurately differentiating CTE from other diseases. Once validated, in vivo CTE biomarkers will facilitate development of criteria for clinical syndrome(s) suggestive of underlying CTE as well as facilitate the development of effective disease-modifying therapies.

Critically, we must also better understand the complicated roles of sex, genetics, and social determinants of health on head trauma-related outcomes and associated biomarkers. There has been considerable optimism in the field that these and other research gaps can be addressed quickly due to ongoing, longitudinal, collaborative research efforts.

#### Breton M. Asken, PhD, ATC

Dr. Asken is a postdoctoral neuropsychology fellow at the Memory and Aging Center, University of California, San Francisco.



#### Michael S. Jaffee, MD, FAAN

Dr. Jaffee is Vice Chair of the Department of Neurology, University of Florida College of Medicine, Gainesville.



## Topic Update

## Treatment of Seizure Disorders

Page B. Pennell, MD

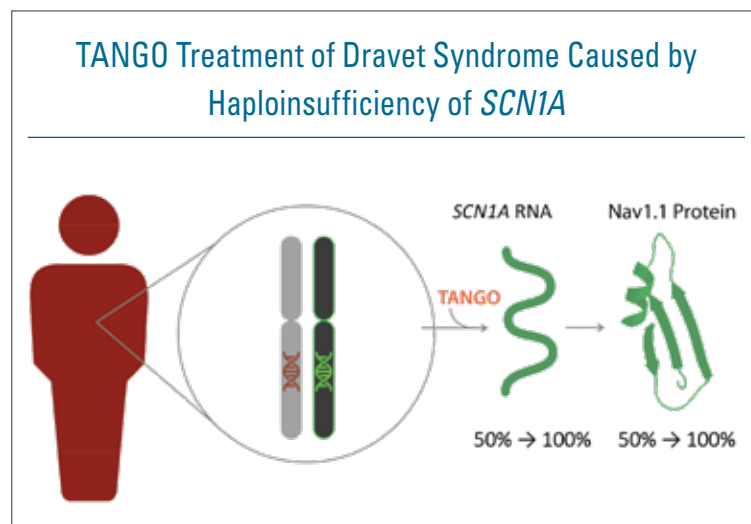
As we turn the corner and look toward a brighter future in 2021, advances in epilepsy give us reason to be hopeful. Recent studies provide evidence that the epileptogenic process can be mitigated in some forms of the disease, gene therapy is getting closer to reality in some epilepsy subtypes, and there is a new promising antiseizure medication (ASM) for focal epilepsy. This new medication has the potential to be superior to the previous 15 medications brought to market as second- and third-generation ASMs. We have gained important insights into epilepsy occurring in special populations, including pregnant women and the elderly. Additionally, technological improvements continue to provide less-invasive strategies for epilepsy surgery. Finally, telehealth has proven to be a new tool for bringing effective outpatient care to our patients with epilepsy and psychogenic nonepileptic seizures (*Epilepsia* 2020; 61:2572). This article provides an overview of these advances in epilepsy care.

For infants with tuberous sclerosis complex (TSC), a multicenter study (EPISTOP) has taken a look at whether the epileptogenic process might be alterable (*Ann Neurol* 2021; 89:304).

Focal seizures and infantile spasms occur in approximately 80% of infants with TSC and are frequently accompanied by intellectual disability and autism. Enrollment included infants <4 months of age who had not previously had a clinical or electrographic seizure. The cohort was followed up until 2 years of age. When epileptiform activity was detected prior to seizures, TSC patients were placed in either a preventive treatment arm with immediate initiation of vigabatrin or a conventional treatment arm with vigabatrin initiation only following the detection of clinical or electrographic seizures. Fifty-four of the 94 enrolled infants had an epileptiform EEG prior to seizures. The time to first clinical seizure was longer in the preventive arm versus the conventional treatment arm (614 vs. 124 days). This study provides rare evidence that the human epileptogenic process can be potentially modified by preventive therapy.

Twenty years ago, the discovery of the cause of Dravet syndrome was one of the first epilepsy-related genetic breakthroughs. Dravet is typically caused by variants in *SCN1A* that result in haploinsufficiency of the voltage-gated sodium channel, Nav1.1. Published results of a recent preclinical study provide hope that gene therapy may be possible in the foreseeable future (*Sci Transl Med* 2020; 12:558). This research group utilized Targeted Augmentation of Nuclear Gene Output (TANGO) technology applied

to a Dravet syndrome mouse model. The approach targets a nonsense-mediated decay exon in *SCN1A* to increase mRNA and protein expression (see figure). The authors demonstrated that a single intracerebroventricular injection of antisense oligonucleotide-22 (ASO-22) at postnatal day 2 restored Nav1.1 protein expression to wild type levels, reduced seizures, prolonged the latency to the first seizure, and dramatically reduced the incidence of sudden unexpected death in epilepsy



Adapted with permission.

(SUDEP). These preclinical findings have the potential to pave the way for ASO gene therapy. A clinical trial has been launched to establish the safety and efficacy of the molecule.

In the treatment of focal seizure, cenobamate was approved by the FDA in 2019 for use in adults. Findings from the phase 3 randomized, controlled, dose-response study were published in 2020. They showed a significant reduction in 28-day seizure frequency (–55% in the 200-mg and 400-mg groups) and dose-dependent increases in the percentage of patients with over 50% reduction in seizures (64% in the 400-mg group). However, the most unique finding compared with other ASM adjunctive trials for focal epilepsy is that 11% and 21% of patients were seizure-free in the 200-mg and 400-mg dose groups during the 12-week maintenance phase.

Epilepsy clinical care can be particularly challenging in special patient populations. Findings from a prospective, observational study published in late 2020 demonstrated that pregnant women with epilepsy had a similar rate of increased seizure frequency (approximately 25%) compared with non-pregnant women with epilepsy (*N Engl J Med* 2020; 383:2547). However, the pregnant women were over six times more likely to have antiepileptic drug (AED) dose changes (nearly all dose increases) during pregnancy compared with nonpregnant women. The dose increases during pregnancy and the decreases seen postpartum closely mirrored prior published results of the pharmacokinetic changes for AEDs during pregnancy.

In the special patient population of the elderly, late-onset epilepsy (LOE) has been the subject of several recent clinical studies. Findings suggest complex interactions between small vessel disease, Alzheimer's disease (AD)–related proteinopathies, and LOE. Some studies support a direct role for hyperexcitability in neurodegenerative disease (*Epilepsy Behav* 2019; 99:106478). Observations shown this past year include elevated cardiovascular risk scores, confluent

white matter hyperintensities, and moderate-to-severe hippocampal atrophy in patients with unexplained LOE (*Clin Neurophysiol* 2020; 131:2667). Additionally, several studies describe the excess risk for dementia after LOE diagnosis — which was elevated threefold in one study (*Neurology* 2020; 95:e3248).

Despite advances in pharmacologic options, one third of patients with epilepsy continue to be drug resistant. Many drug-resistant patients do not access surgery for a variety of reasons, including the reluctance to undergo an open craniotomy. Studies have shown that MRI-guided laser interstitial thermal therapy (MRg-LITT) for mesial temporal lobe epilepsy is a viable option with lower risk and possibly better neuropsychological outcomes compared with open craniotomy for surgical resection (*Epilepsia* 2019; 60:1171; *Ann Neurol* 2018; 83:575; *Epilepsia* 2015; 56:101). The benefit of this approach for other epileptiform foci has been less clear. In one recent small series, MRg-LITT in patients with extratemporal lobe epilepsy showed promising results for eliminating disabling seizure (*Epilepsia* 2020; 61:1723). Extending the utility of MRg-LITT to regions outside of the temporal lobe may provide a critically needed option for this subset of patients with drug-resistant epilepsy.

The many recent advances in our understanding of the epileptogenic process, the course of epilepsy, and the translation to new therapeutic approaches provide optimism for better near-term therapies for the prevention and treatment of epilepsy.

#### Page B. Pennell, MD

Dr. Pennell is Professor of Neurology at Harvard Medical School and Vice Chair of Academic Affairs in the Department of Neurology and a Director of Research for the Division of Epilepsy at Brigham and Women's Hospital, Boston.



## Guideline Watch

# Dementia Prevention and Care — New Guidelines

*An update of 2017 guidelines includes new modifiable risk factors and special Covid-19 considerations.*



## SPONSORING ORGANIZATION

The Lancet Commission on Dementia Prevention, Intervention, and Care

## BACKGROUND AND OBJECTIVE

The Lancet Commission provided a comprehensive report in 2017 on dementia prevention, intervention, and care (*NEJM JW Neurol* Oct 2017 and *Lancet* 2017; 390:2673) and reconvened recently to present updated evidence to prevent, diagnose, and manage dementia. The number of individuals with dementia is expected to increase from 50 million to 152 million between now and 2050, during which time individuals in lower- and middle-income countries (LMICs) are expected to be at higher risk due to increased risk-factor burden. Preventing and delaying the onset of dementia may still reduce global burden, and these updated guidelines add three new modifiable risk factors for dementia: excessive alcohol use, traumatic brain injury (TBI), and air pollution.

## KEY POINTS

### Prevention

Modification of 12 risk factors may prevent or delay 40% of dementias:

- Early life: Less education
- Midlife (45–65 years): Hearing loss, hypertension, obesity, traumatic brain injury (TBI), and alcohol (>21 units/week)
- Late life (>65 years): Smoking, depression, social isolation, physical inactivity, diabetes mellitus, and air pollution

Modification of these risk factors may prevent dementia by reducing neuropathological damage and increasing/maintaining cognitive reserve. Public-health and individually tailored interventions are important. Evidence is strongest for treatment of midlife hypertension with a target systolic blood pressure of <130 mm Hg. Smoking cessation, reduced exposure to second-hand smoke and air pollution, hearing aids, reducing alcohol consumption, prevention of brain injury, reducing obesity, and increased physical activity are recommended. Supplements and vitamins are not recommended. The Mediterranean and Scandinavian diets as well as lifestyle management of sleep may be beneficial. A focus on prevention strategies in LMICs is needed.

### Diagnosis

The neuropathology of dementia remains complex. The 2017 guidelines indicated that timely diagnosis may be aided by history taking, cognitive testing, blood screening, and neuroimaging. These updated guidelines specifically focused on biomarker studies for Alzheimer disease (AD).

- The diagnostic value of biomarkers still needs to be determined.
- Amyloid and tau abnormalities on neuroimaging or in fluid increase the risk for cognitive impairment; however, most cognitively normal people do not develop dementia within a clinically relevant timeframe.

continued

- Negative amyloid biomarkers may be useful in ruling out an underlying AD process.
- Blood biomarkers are currently under investigation.
- High neurofilament light chain levels may be sensitive but not specific for an underlying neurodegenerative process.

#### Intervention and Care

An individualized, humanistic, multidisciplinary approach continues to be recommended for the care of individuals with dementia, though it may be challenging due to a lack of resources.

- After a diagnosis is made, cholinesterase inhibitors may be considered for mild-to-moderate AD, potentially in combination with memantine for moderate and severe AD. Exercise and cognitive training may be beneficial.

The number of individuals with dementia is expected to increase from 50 million to 152 million between now and 2050, during which time individuals in lower- and middle-income countries are expected to be at higher risk due to increased risk-factor burden.

- The approach to managing neuropsychiatric symptoms includes an investigation of potential underlying medical and nonmedical causes, including pain, hunger, and boredom. Medication effectiveness for these symptoms may have variable responses. Sleep medications have not been shown to be effective and may be more harmful to patients with dementia, including an increased risk for falls. Caregiver distress also may be a consequence of neuropsychiatric symptoms and should also be monitored during the care of those with dementia.
- Additional concomitant medical conditions may be associated with faster cognitive decline and decreased quality of life; education of health care professionals is important in communicating with those with dementia.
- Patients with dementia can have worse functional, cognitive, and economic outcomes after a hospitalization. Recognizing that a hospitalized person has dementia is important to optimize care. There is limited high-quality evidence on the management of delirium in those with dementia, although hydration, discontinuing medications that may contribute to delirium, limiting sedation, and optimizing sleep have been strategies to prevent delirium in those without dementia. There is no evidence on the efficacy of medications for treating delirium in those with or without dementia.
- High-quality evidence is limited in end-of-life care for those with dementia. Advanced care planning may decrease caregiver uncertainty. Timely and sensitive information about dementia progression may ameliorate caregiver stress.

### Covid-19 Considerations

- Those with dementia are at higher risk for Covid-19 due to age, concomitant medical conditions, and challenges adhering to safety precautions such as physical distancing.
- Those in LMICs may be at higher risk due to limited resources in testing, protective equipment, and caregiving.
- Recommended public health measures include regular testing of care home staff and residents, appropriate protection for families once visitors are allowed, and consideration of whether to go to the hospital if someone develops severe Covid-19 symptoms.

### Comment

This updated review continues to emphasize the comprehensive, complex nature of dementia prevention, intervention, and care, including during the Covid-19 pandemic. Prevention of risk factors, including excessive alcohol consumption, TBI, and air pollution are important, and the 2020 guidelines emphasize lifestyle modification in modifying these and other risk factors, including sleep disturbances. Further investigation on the appropriateness of biomarkers for diagnostic purposes is still needed.

Another opportunity to reduce the global burden in dementia is to further assess and mitigate inequities of care, especially in LMICs.

### Jennifer Rose V. Molano, MD

Dr. Molano is Associate Professor, Department of Neurology and Rehabilitation Medicine, The University of Cincinnati.

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